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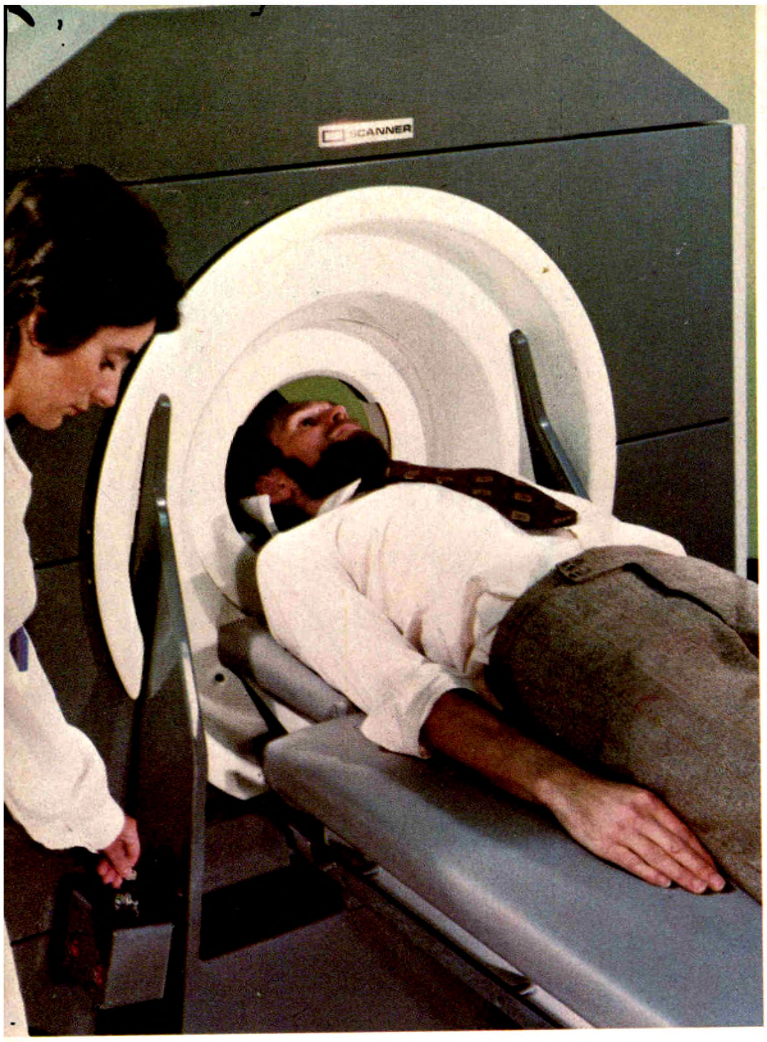

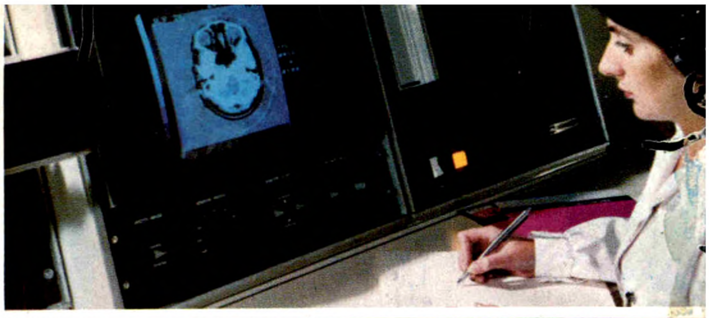

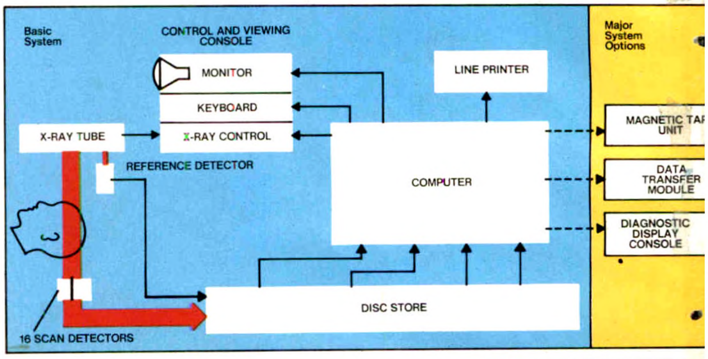

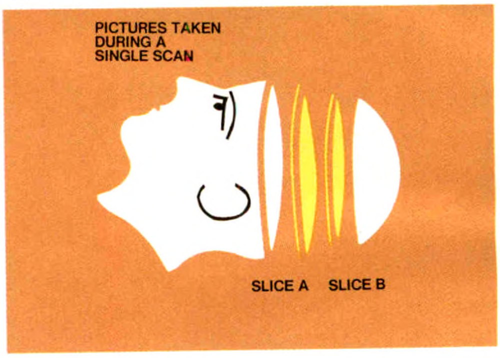
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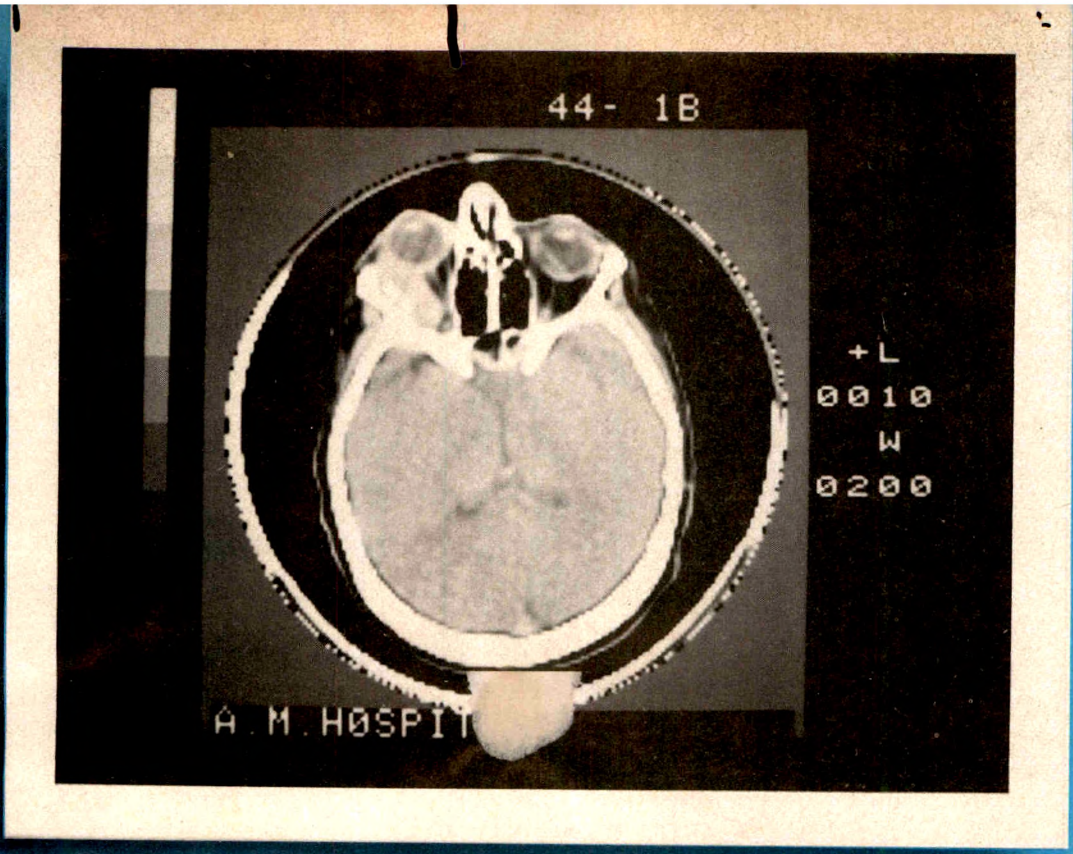

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Archives of Neurology VOL 33, NO. 9, SEPTEMBER 1976

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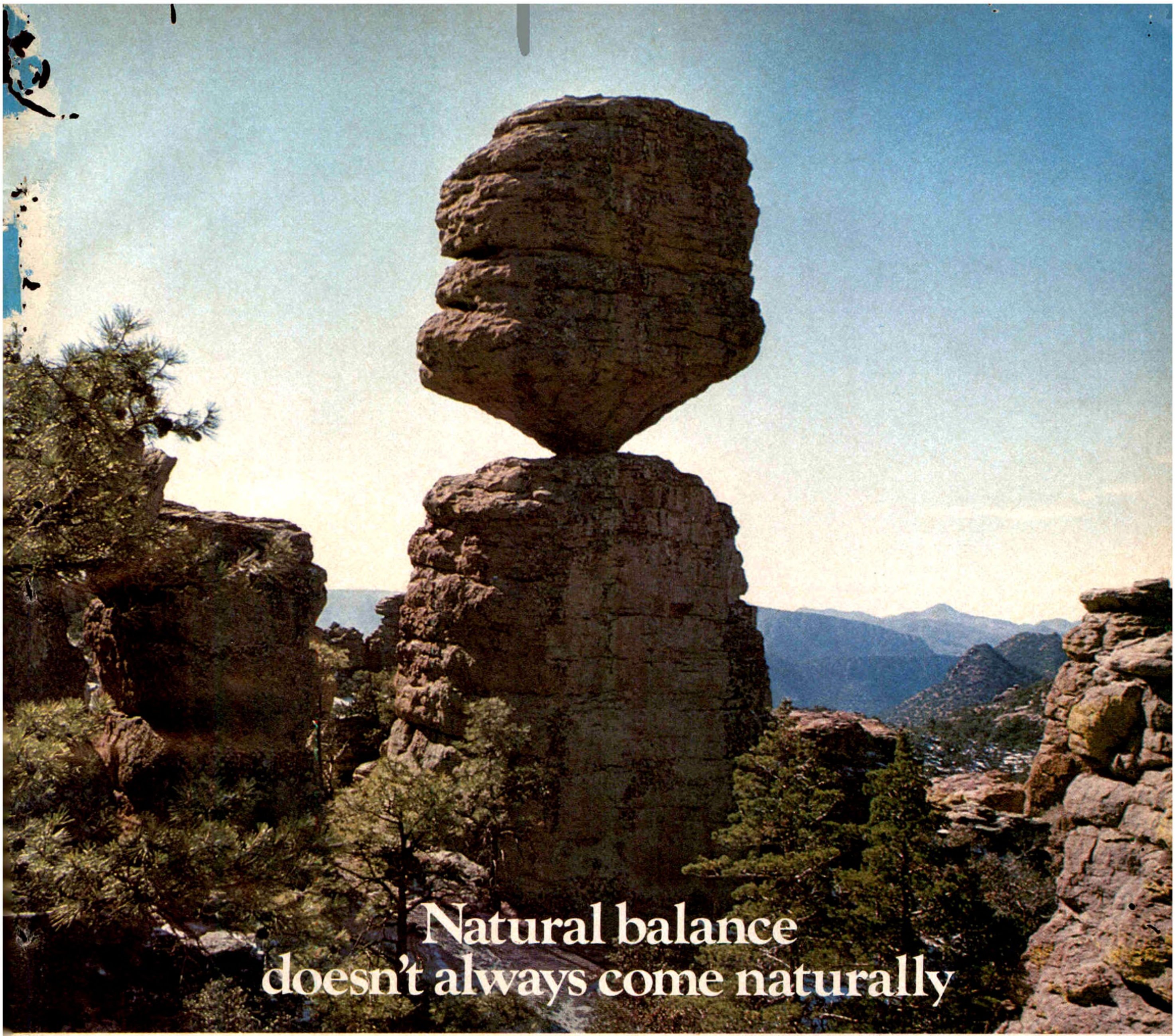

Big Balanced Rock, Chiricahua Mountains, Arizona (approx. 1,000 tons)

■ **Most Widely Prescribed**—Antivert is the most widely prescribed agent for the management of vertigo* associated with diseases affecting the vestibular system such as Menière's disease, labyrinthitis, and vestibular neuronitis.

■ **Relief of Nausea and Vomiting**—Antivert/25 can relieve the nausea and vomiting often associated with vertigo.*

■ **Dosage for Vertigo***—The usual adult dosage for Antivert/25 is one tablet t.i.d.

BRIEF SUMMARY OF PRESCRIBING INFORMATION

> *INDICATIONS. Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:
>
> *Effective:* Management of nausea and vomiting and dizziness associated with motion sickness.
>
> *Possibly Effective:* Management of vertigo associated with diseases affecting the vestibular system.
>
> Final classification of the less than effective indications requires further investigation.

CONTRAINDICATIONS. Administration of Antivert (meclizine HCl) during pregnancy or to women who may become pregnant is contraindicated in view of the teratogenic effect of the drug in rats.

The administration of meclizine to pregnant rats during the 12-15 day of gestation has produced cleft palate in the offspring. Limited studies using doses of over 100 mg./kg./day in rabbits and 10 mg./kg./day in pigs and monkeys did not show cleft palate. Congeners of meclizine have caused cleft palate in species other than the rat.

Meclizine HCl is contraindicated in individuals who have shown a previous hypersensitivity to it.

WARNINGS. Since drowsiness may, on occasion, occur with use of this drug, patients should be warned of this possibility and cautioned against driving a car or operating dangerous machinery.

Usage in Children: Clinical studies establishing safety and effectiveness in children have not been done; therefore, usage is not recommended in the pediatric age group.

Usage in Pregnancy: See "Contraindications."

ADVERSE REACTIONS. Drowsiness, dry mouth and, on rare occasions, blurred vision have been reported.

More detailed professional information available on request.

ROERIG Pfizer
A division of Pfizer Pharmaceuticals
New York, New York 10017

Antivert®/25
(meclizine HCl) 25 mg. Tablets
for vertigo*

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The vulnerable ages

The first epileptic seizure is most likely to occur during early childhood and at the onset of puberty

About 9 out of 10 epileptics experience their first seizure before the age of 20—with the highest incidence between 5 and 7, when children start school, and at the onset of puberty, a time of physiological and psychic turmoil.[1] The most common type, grand mal, occurs in approximately 75% of epileptic children,[1] and more than 50% of patients who suffer initially from petit mal develop grand mal seizures before they reach the age of 16.[2]

Mysoline (primidone) for control of grand mal, psychomotor and focal epilepsy

At the onset and afterwards— used alone or as concomitant therapy, MYSOLINE may reduce the frequency and severity of major motor seizures—or even eliminate them. *Excellent* for control of grand mal. Valuable for control of psychomotor[1,3,4] and focal epilepsy as well.[5]

Add Mysoline when control with other anticonvulsants is inadequate—As concomitant therapy, MYSOLINE can improve seizure control in grand mal and psychomotor epilepsy. The combined use of phenobarbital, diphenylhydantoin, and MYSOLINE may have additive anticonvulsant effects without additive side effects.[6]

Change to Mysoline when other anticonvulsants fail— A changeover to MYSOLINE is frequently warranted when other anticonvulsants must be discontinued because of important side effects, or when grand mal seizures are refractory to phenobarbital, with or without diphenylhydantoin.[7]

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Tablets 250 mg.
50 mg.
Suspension 250 mg./5 cc.

May be the start of a better life for the epileptic

See following page of advertisement for prescribing information.

7538

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may be the start of a better life for the epileptic

initial and maintenance therapy for
grand mal, psychomotor and focal epilepsy

BRIEF SUMMARY
(For full prescribing information, see package circular.)

MYSOLINE® Brand of PRIMIDONE

Anticonvulsant

ACTIONS: MYSOLINE acts on the central nervous system to raise seizure threshold or alter seizure pattern. The mechanism(s) of action of anticonvulsant drugs is not known.

Primidone has anticonvulsant activity *per se.* In addition, its two metabolites possess anticonvulsant qualities. The major metabolite is phenylethylmalonamide (PEMA); the other is phenobarbital. In addition to its own anticonvulsant potential, PEMA potentiates phenobarbital.

INDICATIONS: MYSOLINE, either alone or used concomitantly with other anticonvulsants, is indicated in the control of grand mal, psychomotor, and focal epileptic seizures. It may control grand mal seizures refractory to other anticonvulsant therapy.

CONTRAINDICATIONS: Primidone is contraindicated in: 1) patients with porphyria and 2) patients who are hypersensitive to phenobarbital (see ACTIONS).

WARNINGS: The abrupt withdrawal of antiepileptic medication may precipitate status epilepticus.

The therapeutic efficacy of a dosage regimen takes several days before it can be assessed.

Use in pregnancy: Recent reports strongly suggest an association between the use of anticonvulsant drugs by women with epilepsy and an elevated incidence of birth defects in children born to these women. Reference has been made to primidone in several cases in which it was used *in combination* with other anticonvulsants; but its teratogenicity has not been conclusively demonstrated. The possibility exists that other factors, *e.g.,* genetic factors or the epileptic condition, may contribute to the higher incidence of birth defects. The data also indicate that the great majority of mothers receiving anticonvulsant medication deliver normal infants.

Anticonvulsant drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and risk to both mother and the unborn child.

When the nature, frequency, and severity of the seizures do not pose a clear threat to the patient, good medical practice requires that the physician weigh the expected therapeutic benefit of anticonvulsant therapy against possible risk on an individual basis.

Neonatal hemorrhage, with a coagulation defect resembling vitamin K deficiency, has been described in newborns whose mothers were taking primidone and other anticonvulsants. Pregnant women under anticonvulsant therapy should receive prophylactic vitamin K_1 therapy for one month prior to, and during, delivery.

The physician should weigh all of the foregoing considerations when treating and counseling epileptic women of childbearing potential.

PRECAUTIONS: The total daily dosage should not exceed 2 Gm. Since MYSOLINE therapy generally extends over prolonged periods, a complete blood count and a sequential multiple analysis-12 (SMA-12) test should be made every six months.

In nursing mothers: There is evidence that in mothers treated with primidone, the drug appears in the milk in substantial quantities. Since tests for the presence of primidone in biological fluids are too complex to be carried out in the average clinical laboratory, it is suggested that the presence of undue somnolence and drowsiness in nursing newborns of MYSOLINE-treated mothers be taken as an indication that nursing should be discontinued.

ADVERSE REACTIONS: The most frequently occurring early side effects are ataxia and vertigo. These tend to disappear with continued therapy, or with reduction of initial dosage. Occasionally, the following have been reported: nausea, anorexia, vomiting, fatigue, hyperirritability, emotional disturbances, sexual impotency, diplopia, nystagmus, drowsiness, and morbilliform skin eruptions. Occasionally, persistent or severe side effects may necessitate withdrawal of the drug. Megaloblastic anemia may occur as a rare idiosyncrasy to MYSOLINE and to other anticonvulsants. The anemia responds to folic acid, 15 mg. daily, without necessity of discontinuing medication.

DOSAGE AND ADMINISTRATION: The average adult dose is 0.75 to 1.5 Gm. per day. The initial dose is 250 mg. Increments of 250 mg. are added, usually at weekly intervals, to tolerance, or therapeutic effectiveness, up to daily doses not exceeding 2.0 Gm. A typical dosage schedule for the introduction of MYSOLINE (primidone) is as follows:

Adults and Children Over 8 Years of Age

1st Week 250 mg. daily at bedtime	*2nd Week* 250 mg. b.i.d.
3rd Week 250 mg. t.i.d.	*4th Week* 250 mg. q.i.d.

In children under 8 years of age, maintenance levels are established by a similar schedule, but at one-half the adult dosage. It is best to begin with 125 mg., with gradual weekly increases of 125 mg. a day, to a daily total usually between 500 mg. and 750 mg.

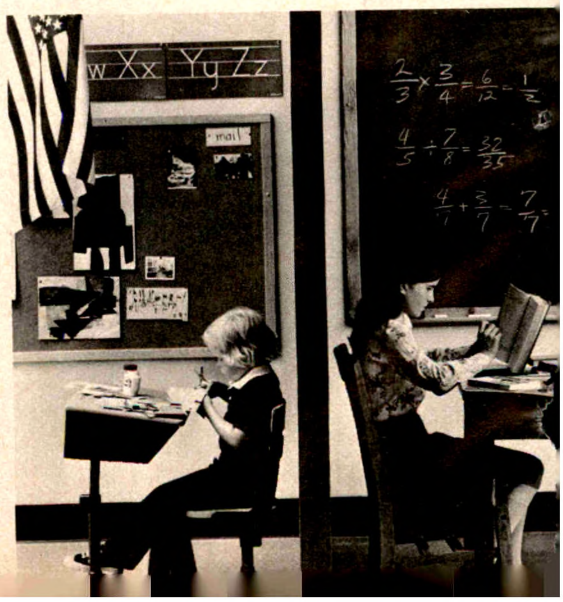
In patients already receiving other anticonvulsants: MYSOLINE should be gradually increased as dosage of the other drug(s) is maintained or gradually decreased. This regimen should be continued until satisfactory dosage level is achieved for combination, or the other medication is completely withdrawn. When therapy with this product alone is the objective, the transition should not be completed in less than two weeks.

MYSOLINE 50 mg. Tablet can be used to practical advantage when small fractional adjustments (upward or downward) may be required, as in the following circumstances:

- for initiation of combination therapy
- during "transfer" therapy
- for added protection in periods of stress or stressful situations that are likely to precipitate seizures (menstruation, allergic episodes, holidays, etc.)

HOW SUPPLIED: MYSOLINE *Tablets*—No. 430—Each tablet contains 250 mg. of primidone (scored), in bottles of 100 and 1,000. Also in unit dose package of 100. No. 431—Each tablet contains 50 mg. of primidone (scored), in bottles of 100 and 500. MYSOLINE *Suspension*—No. 3850—Each 5 cc. (teaspoonful) contains 250 mg. of primidone, in bottles of 8 fluidounces.

References: 1. Livingston, S.: Comprehensive Management of Epilepsy in Infancy, Childhood and Adolescence, Springfield, Ill., Charles C Thomas, 1972, pp. 6, 7, 584. 2. Grossman, H.J.: Ill. Med. J. *135*:260 (Mar.) 1969. 3. Scholl, M.L., in Conn, H.F.: Current Therapy 1973, Philadelphia, Saunders, 1973, pp. 675-7. 4. Metrick, S.: C.M.D. *37*:49 (Jan.) 1970. 5. Forster, F.M.: Med. Clin. North Am. *47*:1579 (Nov.) 1970. 6. White, P.T.: Wis. Med. J. 68:178 (Apr.) 1969. 7. Millichap, J.G.: Drug Ther. *1*:15 (Oct.) 1971.



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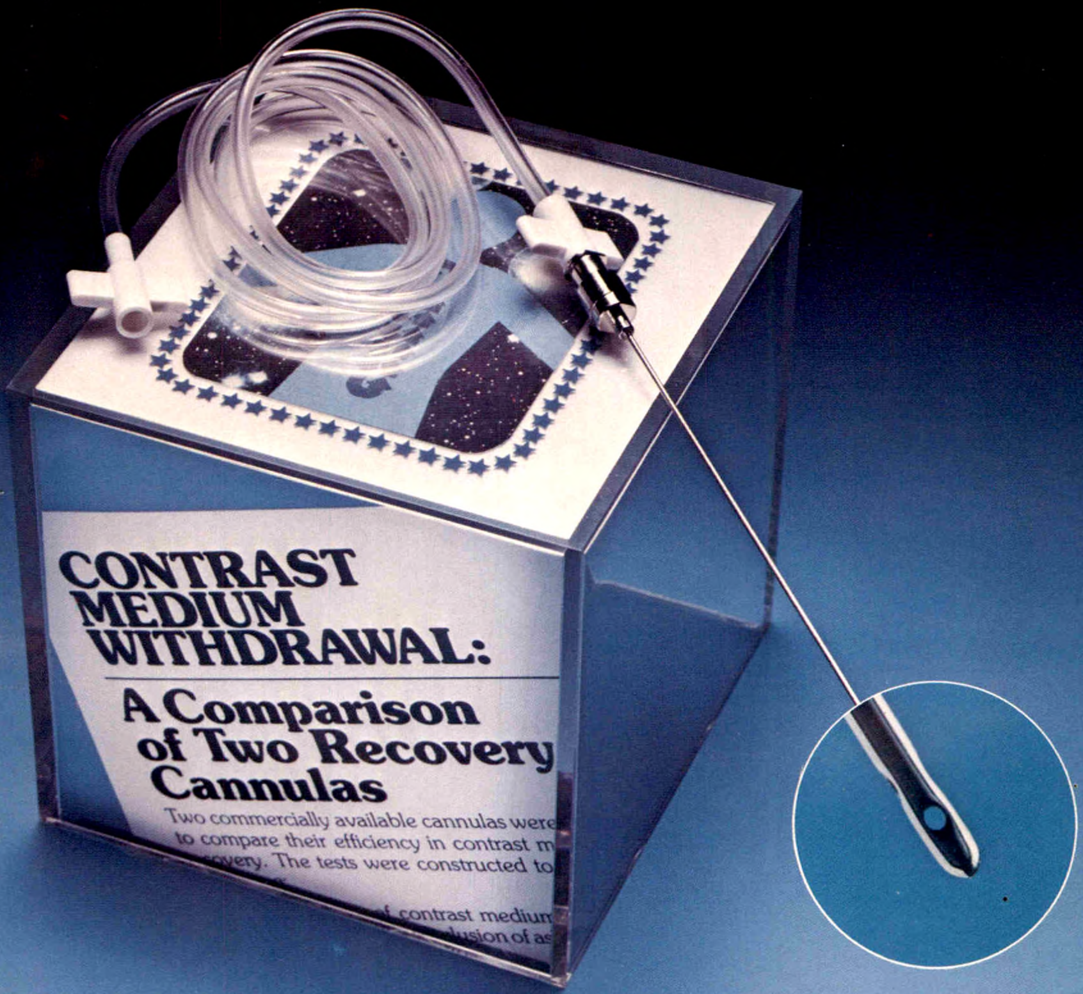
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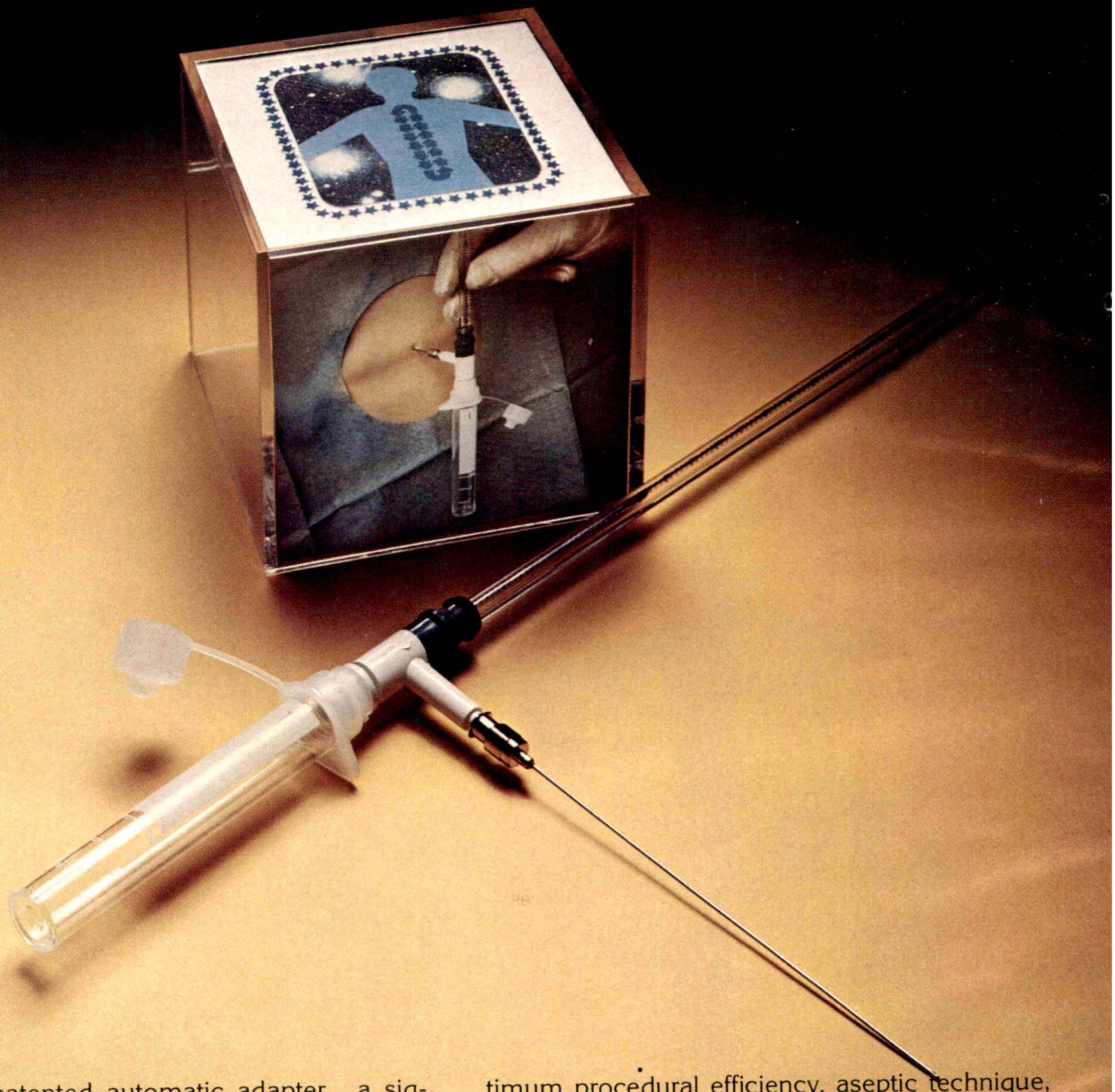

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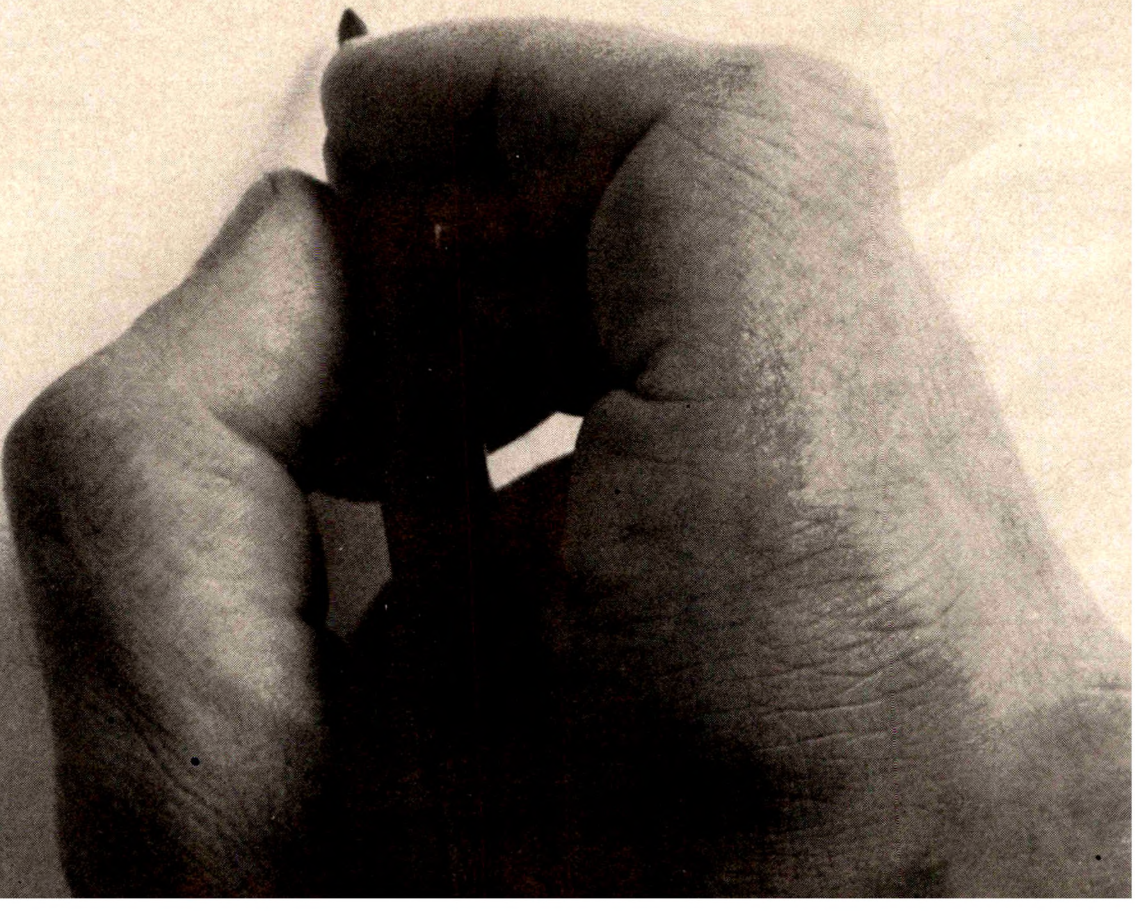
Statistical Review.—Manuscripts containing statistical evaluations should include the name and affiliation of the statistical reviewer.

Tables.—Each table should be typed double-spaced, including all headings, on a separate sheet of 22 × 28-cm (8½ × 11-inch) paper. Do not use larger size paper. If a table must be continued, use a second sheet and repeat all heads and stubs. Each table must have a title.

When drug-induced extrapyramidal symptoms complicate therapy



• TABLETS: 0.5 mg, 1 mg, 2 mg INJECTION: 1.0 mg/ml

COGENTIN®

(BENZTROPINE MESYLATE | MSD)

highly effective against phenothiazine-induced extrapyramidal symptoms

(except tardive dyskinesia)

- **often permits needed chemotherapy to continue by controlling drug-induced extrapyramidal manifestations such as: *tremor, akathisia, motor restlessness, muscular rigidity, drooling, dystonic reactions.***

In some patients, however, the phenothiazine dosage may have to be reduced or discontinued. After one or two weeks, COGENTIN should be withdrawn to determine the continued need for it.

When given concomitantly with phenothiazines or other drugs with anticholinergic activity, patients should be advised to report gastrointestinal complaints promptly; paralytic ileus, sometimes fatal, has occurred in patients taking anticholinergic-type antiparkinsonism drugs, including COGENTIN, in combination with phenothiazines and/or tricyclic antidepressants.

Contraindications: Children under three years of age; use cautiously in older children.

Warnings: Safe use in pregnancy not established. May impair mental and/or physical abilities required for performance of hazardous tasks, such as operating machinery or driving a motor vehicle. When given concomitantly with phenothiazines or other drugs with anticholinergic activity, patients should be advised to report gastrointestinal complaints promptly; paralytic ileus, sometimes fatal, has occurred in patients taking anticholinergic-type antiparkinsonism drugs, including COGENTIN, in combination with phenothiazines and/or tricyclic antidepressants.

Precautions: Because of cumulative action, continued supervision is advisable. Closely observe patients with tendencies to tachycardia and those with prostatic hypertrophy. Dysuria may occur, but rarely becomes a problem. Large doses may cause complaints of weakness and inability to move particular muscle groups, requiring dosage adjustment.

Mental confusion and excitement may occur with large doses, or in susceptible patients; visual hallucinations reported occasionally. May intensify mental symptoms when used to treat extrapyramidal disorders due to neuroleptic drugs (e.g., phenothiazines) in patients with mental disorders; in such patients, increased doses of antiparkinsonian drugs can precipitate toxic psychosis; observe patients carefully, especially at the beginning of treatment or if dosage is increased. Tardive dyskinesia may appear in some patients on long-term therapy with phenothiazines and related agents, or may occur after therapy with these drugs has been discontinued; antiparkinsonism agents do not alleviate symptoms of tardive dyskinesia, and in some instances may aggravate them. COGENTIN is not recommended in tardive dyskinesia.

May produce anhidrosis; give with caution during hot weather, especially to the old, the chronically ill, the alcoholic, those who have central nervous system disease, those who do manual labor in a hot environment, and those with disturbances in sweating. If anhidrosis appears, reduce dosage so that ability to maintain body heat equilibrium is not impaired. Occurrence of glaucoma is a possibility; probably should not be used in angle-closure glaucoma.

Adverse Reactions: Adverse reactions may be anticholinergic or antihistaminic. Dry mouth, blurred vision, nausea, nervousness may develop. If dry mouth causes difficulty in swallowing or speaking, or loss of appetite and weight, reduce dosage, or discontinue drug temporarily. Vomiting occurs infrequently and may be controlled by temporary discontinuation, followed by resumption at a lower dosage. Constipation, numbness of the fingers, listlessness, and depression may develop. Occasionally, an allergic reaction, e.g., skin rash, develops; sometimes this can be controlled by reducing dosage, but occasionally requires discontinuation.

Note: Large doses generally cannot be tolerated by older patients and thin patients. Patients with a poor mental outlook are usually poor candidates for therapy. Do not terminate other antiparkinsonism agents abruptly; reduce gradually. When benztropine mesylate is used with levodopa the usual dose of each may need to be reduced.

How Supplied: Tablets in three strengths: 0.5 mg and 1 mg benztropine mesylate in bottles of 100, 2 mg benztropine mesylate in bottles of 100 and 1000, and 1 mg and 2 mg in single-unit packages of 100; Injection, in 2-ml ampuls, containing per ml: 1.0 mg benztropine mesylate, 9.0 mg sodium chloride, and water for injection q.s.

For more detailed information, consult your MSD representative or see full prescribing information. Merck Sharp & Dohme, Division of Merck & Co., INC., West Point, Pa. 19486

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addendum

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Facts about dosage schedules of COGENTIN (Benztropine Mesylate | MSD)

In treating extrapyramidal symptoms due to neuroleptic drugs, such as phenothiazines and butyrophenones, the recommended dosage of COGENTIN is 1 to 4 mg once or twice a day orally or parenterally. Dosage must be individualized according to the need of the patient. Some patients require more than recommended; others do not need as much. The tablet form should be used when patients are able to take oral medication.

When extrapyramidal symptoms develop soon after initiation of treatment with neuroleptic drugs, they are likely to be transient. One to 2 mg COGENTIN orally two or three times a day usually provides relief within one or two days. After one or two weeks, COGENTIN should be withdrawn to determine the continued need for it. If symptoms recur, COGENTIN can be reinstituted.

Certain extrapyramidal disorders that develop slowly may not respond to COGENTIN. COGENTIN is not recommended in tardive dyskinesia.

For more detailed information, see full prescribing information.

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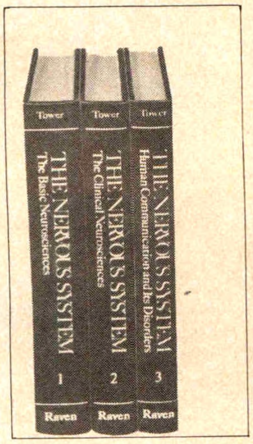

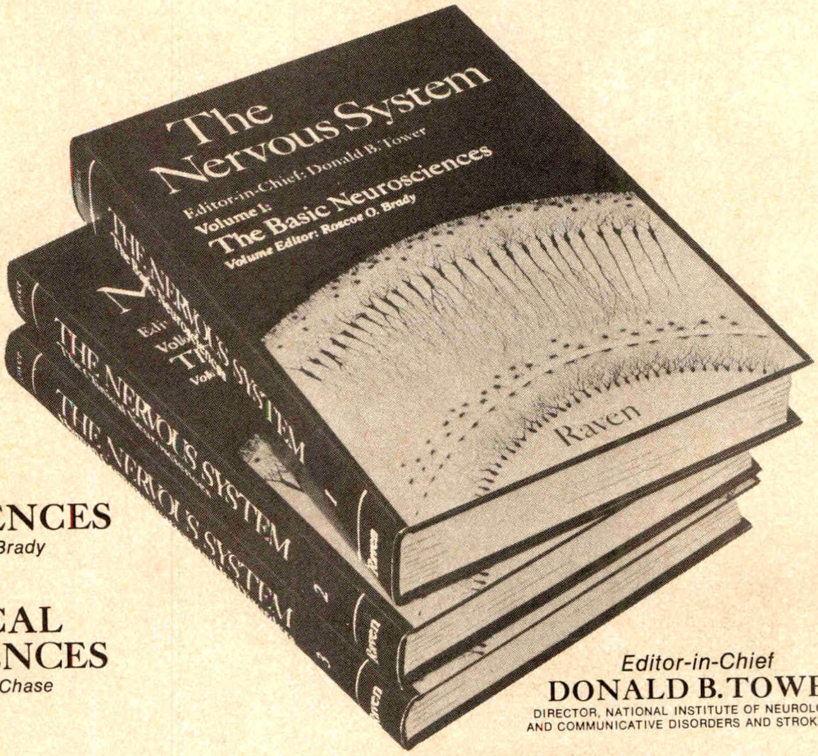

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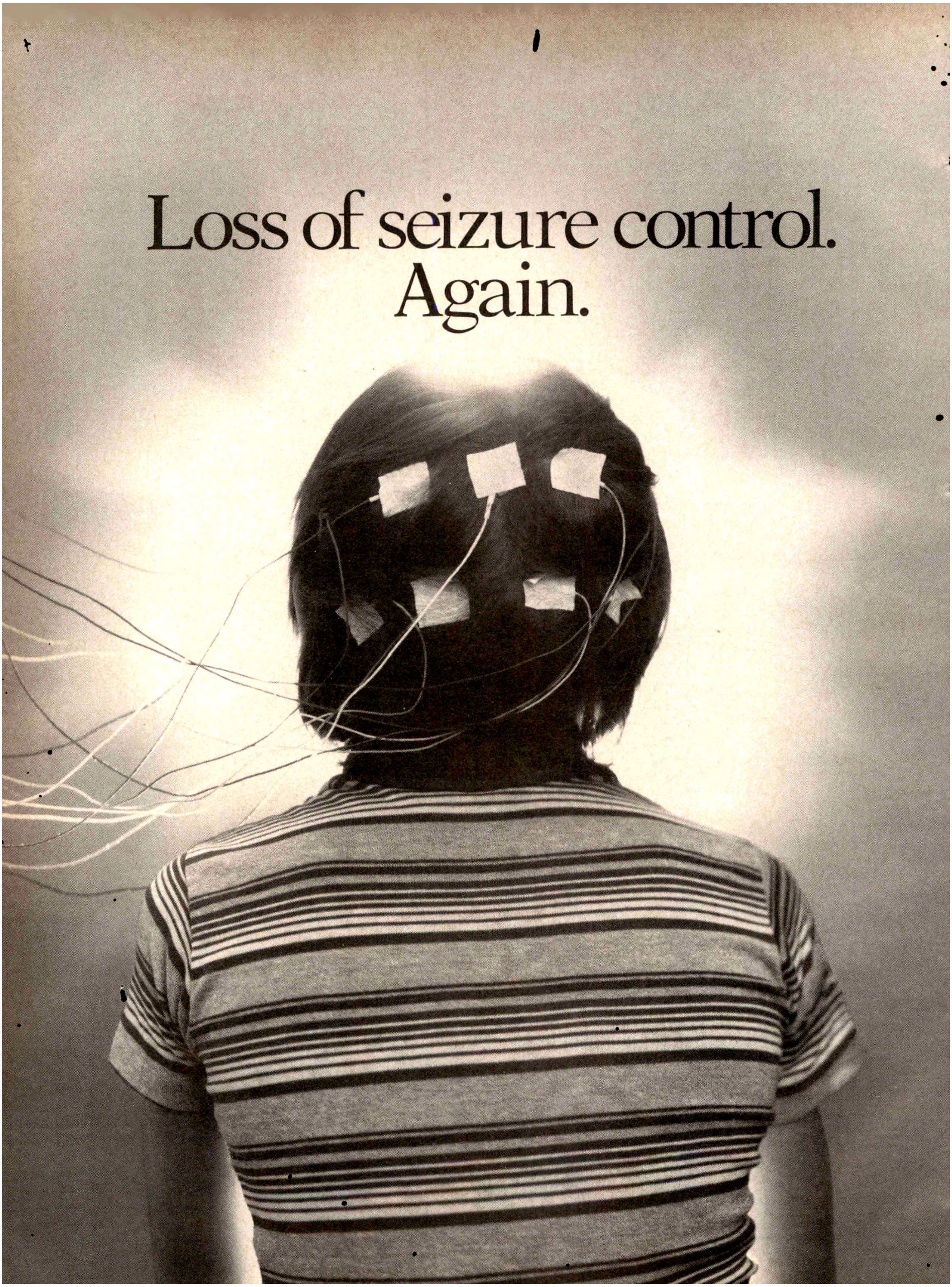
Loss of seizure control.
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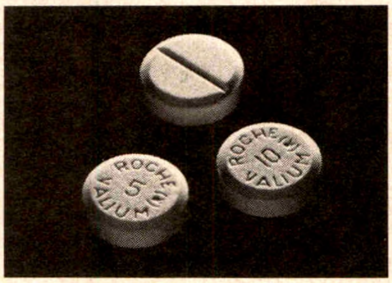
This may be the visit to add oral Valium® (diazepam) to the anticonvulsant regimen.



If the patient is developing tolerance to his usual anticonvulsants, he may benefit from adjunctive Valium (diazepam). Valium—when added to the standard regimen—may help reestablish control of certain seizure disorders. However, Valium has not proved useful as sole therapy.

A particular advantage of Valium is its dosage flexibility. Available in 2-mg, 5-mg and 10-mg *scored* tablets, Valium permits dosage to be easily and conveniently adjusted for maximum therapeutic effectiveness. This is an important consideration in convulsive disorders, where small adjustments in dosage can so often sharply alter the clinical response. The dosage for oral Valium used adjunctively in adults can range from 2 to 10 mg, 2 to 4 times a day. In children, because of their even more varied responses to CNS-acting agents, therapy should be initiated at the lowest dosage—1 mg to 2½ mg, three or four times daily, and increased gradually as needed and tolerated.

In recommended dosage, oral Valium rarely produces significant side effects. When used adjunctively in convulsive disorders, the possibility that Valium may increase the frequency and/or severity of grand mal seizures may require increasing the dosage of standard anticonvulsants. Abrupt withdrawal may have a similar effect.

adjunctive therapy in certain convulsive disorders

Valium® (diazepam) Ⓘⓥ

2-mg, 5-mg, 10-mg scored tablets

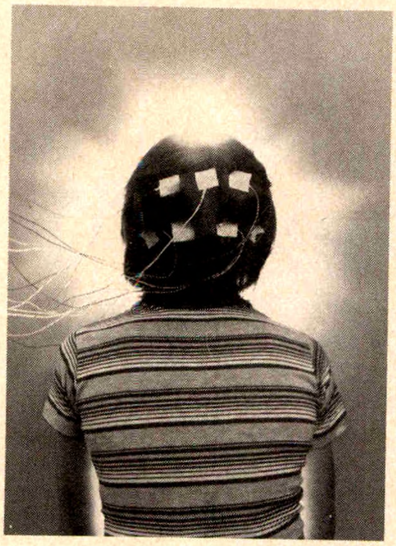
Before prescribing, please see the following page for a summary of complete product information.

adjunctive therapy in certain convulsive disorders

Valium®

(diazepam)

2-mg, 5-mg, 10-mg scored tablets



Before prescribing, please consult complete product information, a summary of which follows:

Indications: Tension and anxiety states; somatic complaints which are concomitants of emotional factors; psychoneurotic states manifested by tension, anxiety, apprehension, fatigue, depressive symptoms or agitation; symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology, spasticity caused by upper motor neuron disorders, athetosis, stiff-man syndrome, convulsive disorders (not for sole therapy).

Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence. In pregnancy, lactation or women of childbearing age, weigh potential benefit against possible hazard.

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

Dosage: Individualize for maximum beneficial effect. *Adults:* Tension, anxiety and psychoneurotic states, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. *Geriatric or debilitated patients:* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) *Children:* 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).

Supplied: Valium® (diazepam) Tablets, 2 mg, 5 mg and 10 mg—bottles of 100 and 500; Tel-E-Dose® packages of 100, available in trays of 4 reverse-numbered boxes of 25, and in boxes containing 10 strips of 10; Prescription Paks of 50, available singly and in trays of 10.

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LEGAL ASPECTS OF NEUROLOGIC PRACTICE

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The following review appeared in the June issue of **The Journal of Legal Medicine:**

"This short but sagacious monograph is oriented exclusively to the medical-legal problems of practicing neurologists and neurosurgeons. It is perhaps of less assistance to lawyers and other physicians. Written from the perspective of a clinical neurologist and containing a wealth of neurological and legal references, it covers a narrow but vital area admirably and fully.

"In the context of the current malpractice crisis, neurologic injuries are apt to be both the most frequent and the most serious. Because of the limited recovery of neural tissue after injury, the inevitable disappointment of patients and families provides fertile ground for lawsuits. Even the most competent practitioners and neurologic centers with the lowest incidence of error have no insulation from threats of malpractice suits. This is the first and only text to fill the acute and immediate need for knowledge that will provide self-protection.

"Like its 12 companion volumes in the Contemporary Neurology Series, it is a sophisticated, balanced, and knowledgeable work, organized in textbook style. The first section is a primer and overview of the law, the courts, and the lawyer's role in our society; it recalls memories of one's undergraduate courses, such as 'Introduction to the Law.'

"Part II, 'The Neurologist in the Court', forms the core of the work and is nothing short of superb. The organization is so extraordinary that no morass of seemingly insoluble problems presents itself. This is not to say that Dr. Beresford has avoided the difficult issues. The unsolved dilemmas of many clinical situations are seen with an experienced eye and described with a skilled mind. For example, in his discussion of the legal requirements of informed consent to drug therapy, he realistically faces the medical difficulties encountered with levadopa, whose side effects approach 100 per cent in frequency and exhibit great variety. In such circumstances, he provides generous references, but clearly restricts the statistics in text so that one is not inundated by a scholarly compendium of irrelevancy.

"Summaries of classic courtroom problems, such as postconcussional syndrome, posttraumatic mental impairment, posttraumatic epilepsy, 'whiplash' injuries, and chronic pain of undetermined origin, are accompanied by landmark case references compiled in no other writing. There are also a multitude of clinical pearls, e.g., the predictable complications of myelograms, cisternograms, angiograms, pneumoencephalograms, and lumbar punctures.

"Finally, there is a fascinating section on more esoteric topics, ranging from legal problems of medical management of violent behavior to those resulting from public relations efforts of selective programs in referral centers. This section contains some thought-provoking questions, fascinating citations, and penetrating analyses.

"The style is workmanlike and efficient, although lacking in the grace and elegance of language that create excitement. Sometimes strain is evident in providing credibility for both sides of a problem. For the most part, however, the mucky dilemmas are beautifully summarized.

"This monograph precisely defines, thoroughly illuminates, and thoughtfully discusses the topic at hand. Its masterfully selected references will keep it on the reference shelf in both hospitals and offices. It is nearly certain to be a classic for every neurologist and neurosurgeon and should be read avidly 'before dawn tomorrow.' "

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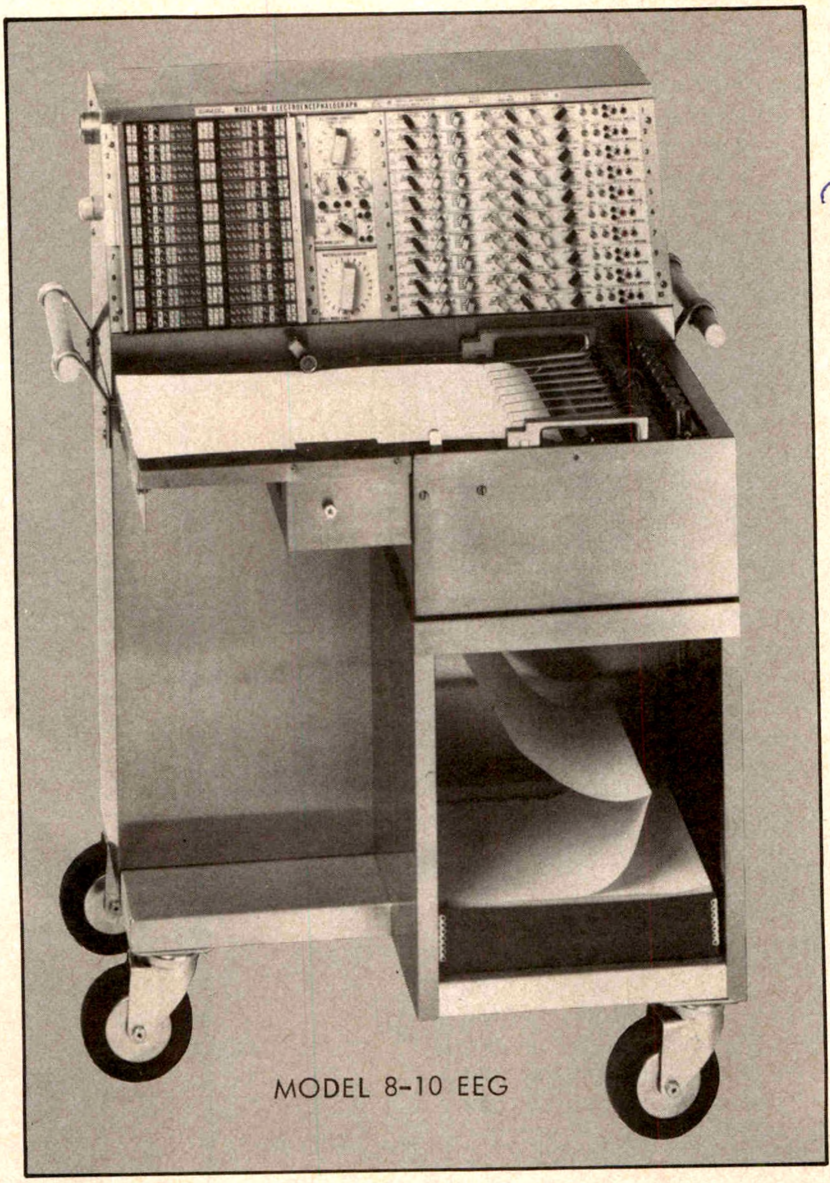

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Enough carbidopa

A daily dosage of SINEMET should be chosen that will provide approximately 70 to 100 mg of carbidopa because studies show that peripheral dopa decarboxylase is saturated by carbidopa at approximately 70 to 100 mg per day.

SINEMET-25/250 is the most convenient strength for providing the proper amount of carbidopa necessary for optimal therapeutic response. For example, one SINEMET-25/250 t.i.d. provides 75 mg of carbidopa—an adequate amount of carbidopa for maximum utilization of levodopa with less nausea and vomiting.

Enough levodopa

A daily dosage of SINEMET should be chosen that will provide approximately 25 percent of the previous levodopa daily dosage.

SINEMET-25/250 is the most convenient strength for providing the proper amount of levodopa. For example, one SINEMET-25/250 t.i.d. provides 750 mg of levodopa—the proper amount of levodopa for patients previously on 3000 mg of levodopa. (Please refer to the addendum for dosage guidelines for patients who are not on levodopa or who have been taking less than 1500 mg per day.)

Other dosage considerations

Discontinue levodopa at least 8 hours before SINEMET is begun. A time interval shorter than 8 hours may increase the risk of levodopa-induced adverse reactions.

Because of increased brain dopamine levels, both therapeutic and adverse reactions (specifically, involuntary movements and mental disturbances), occur at lower doses and more rapidly with SINEMET than with levodopa. In order to reduce adverse reactions, it is necessary to individualize therapy and to monitor the patient closely during the dose adjustment period. The occurrence of involuntary movements may require dosage reduction. Blepharospasm may be a useful sign of excess dosage in some patients.

Instruct patients not to take levodopa with SINEMET unless you specifically recommend it.

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Dosage Guideline

Addendum

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Maximum dose: 8 tablets of SINEMET-25/250 daily. Alternatively, dosage may be titrated to 6 tablets of SINEMET-25/250 a day, and further adjusted with increments of levodopa.

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containing 10 mg carbidopa and 100 mg levodopa

For patients who are not on levodopa or for patients on levodopa who have been taking less than 1500 mg per day:
Start with SINEMET-10/100 t.i.d. and increase by 1 tablet every day or every other day until a dosage of 6 tablets is reached. If further titration is necessary, *change* the patient to SINEMET-25/250, at a dosage of 1 tablet t.i.d.
NOTE: Most patients on SINEMET will eventually require SINEMET-25/250 for optimal control of the symptoms of Parkinson's disease.

For full details of dosage and administration see prescribing information.

Sinemet®

a combination of carbidopa and levodopa

can mean a world of difference for some parkinsonian patients

When SINEMET is to be given to patients who are being treated with levodopa, levodopa must be discontinued at least 8 hours before therapy with SINEMET is started. In order to reduce adverse reactions, it is necessary to individualize therapy. See the Warnings (below) and Dosage and Administration sections in the full prescribing information before initiating therapy.

Contraindications: MAO inhibitors and SINEMET should not be given concomitantly. MAO inhibitors must be discontinued at least 2 weeks prior to initiating therapy with SINEMET.

SINEMET is contraindicated in patients with known hypersensitivity to this drug and in narrow-angle glaucoma.

Because levodopa may activate a malignant melanoma, it should not be used in patients with suspicious, undiagnosed skin lesions or history of melanoma.

Warnings: Levodopa must be discontinued at least 8 hours before SINEMET is started. SINEMET should be substituted at a dosage that will provide approximately 25 percent of the previous levodopa dosage. (See Dosage and Administration section of full prescribing information.) Patients taking SINEMET should be instructed not to take additional levodopa unless prescribed.

As with levodopa, SINEMET may cause involuntary movements and mental disturbances. These reactions may be due to increased brain dopamine following administration of levodopa. All patients should be observed carefully for development of depression with concomitant suicidal tendencies. Treat with caution patients with past or current psychoses. *Because carbidopa permits more levodopa to reach the brain and, thus, more dopamine to be formed, dyskinesias may occur at lower dosages and sooner with SINEMET than with levodopa.* Occurrence of dyskinesias may require dosage reduction.

SINEMET should be administered cautiously to patients with severe cardiovascular or pulmonary disease, bronchial asthma, renal, hepatic or endocrine disease.

Exercise care in administering SINEMET, as with levodopa, to patients with history of myocardial infarction who have residual atrial, nodal, or ventricular arrhythmias. In such patients, cardiac function should be monitored with particular care during period of initial dosage adjustment, in a facility with provisions for intensive cardiac care.

As with levodopa, there is possibility of upper G.I. hemorrhage in patients with history of peptic ulcer.

Usage in Pregnancy and Lactation: Although effects of SINEMET on human pregnancy and lactation are unknown, both levodopa and combinations of carbidopa and levodopa have caused visceral and skeletal malformations in rabbits. Use of SINEMET in women of childbearing potential requires that anticipated benefits of the drug be weighed against possible hazards to mother and child. SINEMET should not be given to nursing mothers.

Usage in Children: Safety of SINEMET in patients under 18 has not been established.

Precautions: As with levodopa, periodic evaluations of hepatic, hematopoietic, cardiovascular, and renal function are recommended during extended therapy.

Patients with chronic wide-angle glaucoma may be treated cautiously with SINEMET provided intraocular pressure is well controlled and patient is monitored carefully for changes in intraocular pressure during therapy.

Symptomatic postural hypotension can occur. For this reason, SINEMET should be given cautiously to patients on antihypertensive drugs. When SINEMET is started, dosage adjustment of the antihypertensive drug may be required. (For patients receiving pargyline, see the contraindication on MAO inhibitors.)

Since phenothiazines and butyrophenones may reduce therapeutic effects of levodopa, they should be administered with caution if concomitant administration with SINEMET is necessary, and patients should be carefully observed for loss of antiparkinsonian effect.

Adverse Reactions: Most common serious adverse reactions occurring with SINEMET are choreiform, dystonic, and other involuntary movements. Other serious adverse reactions are mental changes including paranoid ideation and psychotic episodes, depression with or without development of suicidal tendencies, and dementia. Convulsions also have occurred; however, a causal relationship with SINEMET has not been established.

A common but less serious effect is nausea.

Less frequent adverse reactions are cardiac irregularities and/or palpitations, orthostatic hypotensive episodes, bradykinetic episodes (the "on-off" phenomenon), anorexia, vomiting, and dizziness.

Rarely, G.I. bleeding, development of duodenal ulcer, hypertension, phlebitis, hemolytic anemia, leukopenia, and agranulocytosis have occurred.

Other adverse reactions reported with levodopa include dry mouth, dysphagia, sialorrhea, abdominal pain and distress, ataxia, increased hand tremor, headache, numbness, weakness and faintness, bruxism, confusion, insomnia and nightmares, hallucinations and delusions, agitation and anxiety, malaise, fatigue, euphoria, muscle twitching and blepharospasm (may be taken as an early sign of excess dosage; consider dosage reduction at this time), trismus, burning sensation of tongue, bitter taste, diarrhea, constipation, flatulence, flushing, skin rash, increased sweating, bizarre breathing patterns, urinary retention, urinary incontinence, diplopia, blurred vision, dilated pupils, hot flashes, weight gain or loss, dark sweat and/or urine, oculogyric crises, sense of stimulation, hiccups, edema, loss of hair, hoarseness, priapism, and activation of latent Horner's syndrome.

Abnormalities in laboratory tests may include elevations of blood urea nitrogen, SGOT, SGPT, lactic dehydrogenase, bilirubin, alkaline phosphatase, protein-bound iodine, and positive Coombs test. More commonly, levels of blood urea nitrogen, creatinine, and uric acid are lower during administration of SINEMET than with levodopa.

Overdosage: Management of acute overdosage with SINEMET is basically the same as management of acute overdosage with levodopa; however, pyridoxine is not effective in reversing the actions of SINEMET.

How Supplied: Tablets SINEMET-10/100 and Tablets SINEMET-25/250 are supplied in bottles of 100.

For more detailed information, consult your MSD representative or see full prescribing information, Merck Sharp & Dohme, Division of Merck & Co., INC., West Point, Pa. 1948

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Editorial

Resource Allocation for the Severely Brain Damaged

The Archives has usually left to more general journals the important, but by nature imprecise, examinations of medicine's responsibilities to the larger public and we, by and large, plan to continue such a policy. The subject of the following article, however, has become a major issue in the contemporary neurological world, for the outcome of the enormous expenses of "critical care" must be judged by not only the relatively low survival rate (N Engl J Med *294:982-986, 1976), but by the neurological capacities of the survivors as well. Accordingly, the Editors believe that Professor Jennett's thoughtfully expressed point of view deserves wide attention by those involved with care of the severely brain-damaged of any age. Needless to say, the subject has stimulated varying opinions among ourselves and we expect that it will do so among our readers, whose views on this important issue are welcome.—Ed.*

There are physicians who deny that the allocation of resources has anything to do with them—even in countries where health is a community concern, and the people look to physicians for advice, if not for leadership, in the distribution of health care. The physician's slogan, "my job is to spend money not to save it," may sound a clarion call to the patients immediately around him, but it can be a death knoll for those who are denied the benefits of appropriate care by his spendthrift attitude. If resources were unlimited, such an attitude might be defensible, but with the current cost of modern medical care, there is no country where that is so today.

It is true that much of the allocation of money for patient care takes place at levels beyond the sphere of influence of physicians, who can therefore afford the luxury of being uninvolved. It is others who decide what proportion of the budget goes to health, to education, or to defense; and even in the Health Department, where priorities are decided between acute medicine and prevention, between hospital services and community care, between one hospital discipline and another, clinicians are not involved. But physicians dealing with the critically ill know only too well that it is they, and they alone, who have the difficult job of allocating the restricted resources placed at their disposal by others—by government, by health administrators, and by their own hospital colleagues.

How is this done? Too often it is on the "first come" principle. This acknowledges the human and understandable fact that physicians (and even more nurses) feel a commitment to patients whom they have already begun to treat—for them they feel a responsibility, but for the patient they have not yet seen, they do not. When a new patient arrives and the ward is full, it is often difficult to persuade the staff to look at all the patients already in the ward and to consider whether one of them should be discharged because he is unlikely to derive further benefit from retention in intensive care, either because he is too badly affected or because he is already sufficiently improved. For the latter kind of patient, as for the newcomer, the standard of alternative care available is crucial; in some hospitals, there nowadays seems not much middle ground left between intensive care and relative neglect, even if this is styled by the more positive label of "self-help." The only rational basis for selection is "who will most likely benefit from intensive care," or "who will be least harmed by having to do with a lesser standard of care?" Everyone agrees that the brain-dead patient must not be maintained once the diagnosis is made, but as Skillman[1] has stated, "the enormous pressure to obtain intensive care for all critically ill patients forces us to make decisions about discontinuation of care before the brain is irreversibly dead." This is not only a matter of economics; to quote Skillman again, "Evasion of this responsibility in the intensive care unit produces a serious deterioration in the morale of personnel." This kind of difficult decision may be facilitated by the evolution of a general policy, by prior agreement, at a time when choices between actual patients are not being made. The principles involved apply equally when admission to, or retention in, a special rehabilitation unit is under discussion, although the decision may then seem less critical because there is more time to make it.

Intensive care of any kind is expensive and scarce. For conditions that have a high mortality even with such care, such as severe brain damage, even more expensive regimes are proposed from time to time—desperate diseases demand desperate remedies. Advocates may advance theoretical arguments as to why benefits should accrue from such treatment (eg, prolonged artificial ventilation for head-injured patients), and they may describe patients whom it is claimed have benefited. Even if this evidence is convincing, there are three questions that should be satisfactorily answered before this, or any other new method, is accepted as the proper treatment for a given category of patients: (1) Is the new method more effective than established ones? (2) Is it better enough to justify the extra cost, taking into account the probability that it will be unsuccessful? (3) Is the extra benefit deriving from deployment of resources on this new activity needed more than that which it displaces—assuming a fixed budget? The individual clinician cannot himself answer these questions, but they are more than rhetorical if they serve to remind him of the consequences of too readily recommending that many patients should be treated in some elaborate and expensive way on the basis of a clinical impression based on the supposed benefit gained by random cases. Medicine today abounds in the inappropriate use of expensive treatment. It may be (1) unnecessary (the condition is not bad enough), (2) unsuccessful (the condition is too bad or advanced), (3) unsafe (there are too many complications), (4) unkind (the quality of life of the survivors is not acceptable), or (5) unwise (a diversion of resources). This brings us from the general to the particular—to the dilemma of expending resources on the badly brain damaged patient. Because it is in field of brain damage that patients are often the recipients of treatment that is unsuccessful and unkind, which then makes the diversion of resources unwise.

In the specific context of head injury, a series of milestones can be recognized in each of the last four decades. Cairns,[2] in 1947, commented that reflection on his war experience led him to conclude that some who survived were so crippled that they would have been better dead. A decade later the mortality of civilian head injuries was halved by respiratory intensive care, and those who first reported this believed that most survivors would recover well and return to work.[3] A decade later it again became clear that this had been heady optimism; London[4] reported that British hospitals were discharging 1,500 permanently brain damaged survivors of head injury every year, their average age 30 years, and half of them never to work again. The usual defense of physicians is that many patients whom they thought had looked equally bad had made good recoveries, so everyone had to be treated as potentially recoverable. There is promise that by the end of the present decade (1977), it may be possible to put prognosis in this field on a formal basis. This is the purpose of a transatlantic study into the prognosis of coma, supported by the National Institutes of Health, which deals with the probability of various outcomes expressed in numerical form, both after severe head injury[5] and after nontraumatic coma.[6] If indeed we can learn to recognize the probable outcome soon after an ictus of brain damage, it will become possible more often to ensure that restricted resources are concentrated on those patients who both need intensive treatment and are likely to benefit from it.

This approach implies not only an ability to predict the likely outcome that will result from alternative courses of action, but a willingness to make a judgment about the relative values of different states of health that may result from severe brain damage. The real size and seriousness of the problem of persisting disability after brain damage is apt to remain concealed under a blanket of euphemisms. Unduly optimistic assessment is liable to be made because physical handicaps may not be great, whereas it has been clearly shown that mental disability contributes much more significantly to the overall social outcome.[7] A simple scale by which to judge this social outcome after brain damage has been described,[8] which has proved useful in practice. Four categories of survival are recognized—the vegetative state,[9] the severely disabled (conscious but dependent), the moderately disabled (independent but disabled), and good recovery. What level on this scale should be regarded as an acceptable result of treatment is obviously a value judgment—and that will depend on who is the judge. There is now a growing awareness of the importance of the quality of life in survivors of major illness (eg, leukemia and other malignant neoplasms treated by chemotherapy) and with this goes the implication that there are some states of survival that may be judged worse than death.

An attempt has been made to test opinion about states of survival after brain damage by asking groups of people to record anonymously which they considered to be worse, for the patient and also for the family, of two pairs of outcomes—death or vegetative survival, and vegetative survival or severe disability. This was asked of 130 senior health professionals and lawyers attending a meeting on severe brain damage in San Francisco; and a week later it was administered to 130 medical students who were in their first year of clinical studies in Glasgow, Scotland. In spite of the wide difference in age and experience, the responses were surprisingly similar; about 90% regarded vegetative survival as worse than death, and over 40% considered that to regain consciousness but to be dependent would be worse than the vegetative state for the patient himself; but less than 20% of respondents thought the family would think this. Subsequent surveys among nurses and general practitioners in Britain, and among nurses and students in the Netherlands, show a similar pattern. This kind of questionnaire approach can be critcicized on philosophical and theoretical grounds, but in view of the consistent response, it is difficult to escape the conclusion that many people are now willing to admit that survival after severe brain damage may be judged a disaster for the victim and his family. It is the combination of mental impairment with physical handicap that makes disability after brain damage so devastating, not only for the patient but for the family, who may indeed bear most of the burden, especially if the patient has limited insight. Comparisons with the heroic and often happy survival of patients with spinal paralysis, who are mentally intact, are for this reason irrelevant.

It is inevitable that the attempt to save the lives of badly brain damaged patients will not always be successful; part of the price paid for the good recoveries, of which there are many, is that some others will be left so badly crippled that sensitive observers may judge their survival a greater disaster than if they had died. Both physicians and society at large need to be aware of this price, and to consider from time to time whether it is too high. Acceptance of the principle that survival at any price is no longer an acceptable objective gives a new perspective to the allocation of resources in the realm of medical care for the critically ill. It is no longer a matter of ensuring that as many patients as possible get all available treatment, which it is presumed can do only good. There is now need to protect patients and their families from suffering emotionally and financially from too much treatment—quite apart from the benefit denied to others by the diversion of resources to patients who do not stand to gain. It would be ironic if society were to encourage physicians to dissipate the resources of the community in this way by the threat to litigate whenever all efforts are not made to use extreme and protracted means of resuscitation and support, regardless of the circumstances. This situation is one of our own creation, a child of technological advance, and it is hardly surprising that such artifacts of nature shoudl be beyond the capacity of traditional ethics and morality to deal with. New technology needs new moral, ethical, and, eventually, legal thinking. Only when these topics are responsibly discussed in public debate, and perhaps in courts of law, will it become possible for individual physicians to discuss the matter in relation to particular patients about whom decisions have to be made, because whatever their private views, few physicians or lay people will dare to move far ahead of the general consensus of the society of which both are a part. Certainly there are countries where this has already happened to a large extent, for example, in Britain and the Netherlands; in both of these, it is philosophers and theologians who have led the move toward a more realistic acceptance of the new situation. In neither country is litigation an issue of more than minor significance, and therefore lawyers have not figured prominently in the debate.

Under the title "Protecting the Medical Commons," Hiatt[10] has recently written lucidly about the question of the inappropriate allocation of medical resources. He draws an analogy with the herdsman with animals grazing on common land—as long as pasture is plentiful, each herdsman can increase his holding without detriment to the general welfare. Not so once capacity is approached; when "freedom on the common brings ruin to all." This is today's doctor's dilemma: he can no longer afford the luxury of always doing everything for every patient, regardless of the consequences for others, or for society. And he certainly should question the utilization of precious resources for practices that benefit neither the individual nor society.

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Original Contributions

Ribonuclease Treatment of Tick-Borne Encephalitis

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• Clinical trials of the pancreatic ribonuclease (RNAse) in treatment of patients with tick-borne encephalitis were carried out. Two hundred forty-six patients were treated with RNAse and 261 were given antiencephalitic gamma globulin. Administration of 30 mg of RNAse every four hours over a period of five to six days provided stable high concentrations of the enzyme in blood that exceeded normal values by two to three times. An increase of RNAse activity in cerebrospinal fluid also took place. The comparison of RNAse and gamma globulin demonstrated a considerable advantage of the former: under RNAse treatment the temperature normalized on the average of twice as quickly, and a rapid regression occurred in meningeal symptoms and cerebrospinal fluid pleocytosis. In patients treated with RNAse, no adverse reactions or aftereffects were observed. On the grounds of the reported results, RNAse was accepted officially as a new, highly efficient antiviral drug for the treatment of tick-borne encephalitis.

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It is well established that when a virus enters the cell, its nucleic acid is freed from its protein coat and serves as a template for the replication and synthesis of viral proteins. These processes provide for the formation of new viral particles at the expense of cell materials and energy. The infected cells are either damaged or killed, and new viral particles attack intact cells.[1,2] The viral nucleic acids that are liberated from their protein coats within the cell are much more susceptible to the injurious action of exogenous nucleases than when protected by protein capsids.[3] The degradation of the molecules of viral nucleic acid by nucleases may interfere with the replication, transcription, and, consequently, with the multiplication of the virus.

One of the authors (R.I.S.), with coworkers, has previously shown that the addition of pancreatic deoxyribonuclease (DNAse, EC 3.1.4.5) to virus-infected tissue culture will inhibit the DNA synthesis and reproduction of such DNA-containing viruses as the adenovirus, vaccinia, and herpesviruses.[4-6] Special experiments have shown that in the concentrations used, DNAse does not inhibit host-cell DNA synthesis or delay mitoses, and causes no chromosome aberrations.[7] These studies served as the bases for clinical tests that have shown a high efficiency of DNAse in adenoviral conjunctivitis,[8] herpetic keratitis, including the most severe 5-idoxuridine-resistant forms,[9] and in herpes zoster.[10] On these grounds DNAse was officially permitted in this country for clinical use as a new antiviral drug.

Ribonuclease (RNAse, EC 3.1.4.1) was shown to inhibit RNA synthesis and the reproduction of such RNA-containing viruses as influenza,[11-13] foot and mouth disease, and tick-borne encephalitis viruses.[6,14] Parenteral administration of RNAse increases significantly the survival of mice infected with tick-borne encephalitis virus.[14] Antiviral concentrations of RNAse do not damage tissue culture cells, and have no toxic or teratogenic effects when administered to animals.[15] These investigations have prompted clinical studies of RNAse in tick-borne encephalitis and other viral diseases. The results of the studies are presented in this article. Preliminary data have been published elsewhere.[16]

SUBJECTS AND METHODS

The studies were carried out from 1965 through 1971 in four areas of this country

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Reprints not available.

where outbreaks of the disease sometimes occur: in some regions of Western Siberia—Novosibirsk and Kemerovsk districts; in the Ural—Sverdlovsk district; and in the Far East—Khabarovsk district; by different groups of physicians under the guidance of the authors, using identical clinical criteria and the same method of treatment. Five hundred seven patients with tick-borne encephalitis were studied. Only those patients were treated whose diagnosis of tick-borne encephalitis was corroborated serologically. Of these, 246 were treated with RNAase, and 261 were given antiencephalitic gamma globulin.

Commercially obtained sterile pancreatic RNAse was used. The RNAse was isolated from beef pancreas, sterilized, and lyophilized. The specific activity of RNAse was 7 × 10^6 units/gm. One unit of activity is equal to the amount of RNAse that hydrolyzes 1 mg of yeast RNA to acid-soluble oligonucleotides for one hour. Gamma globulin was prepared from horse serum obtained from animals hyperimmunized by a mixture of tick-borne encephalitis viruses of different strains. The titer of the specific antiviral activity of the preparations used was 1:3,000. For intramuscular administration, 30 mg of sterile RNAse was dissolved in 3 ml of saline and was administered every four hours, usually for four to six days. The treatment of patients began on the first day of admission to hospital, as a rule on the second or third day of the disease, and was stopped after temperature had normalized for two days. The average dose was 180 mg of RNAse per day; it took about 800 to 1,000 mg of the preparation for a course of treatment. Antiencephalitic gamma globulin was administered intramuscularly, 6 ml daily for three days. In addition, all patients received symptomatic remedies.

The efficiency of the preparations was estimated by: (1) the duration of the febrile period; (2) the time required for normalization of temperature from the beginning of treatment; (3) temperature decrease during the first 24 hours of treatment; (4) the time required for disappearance of meningeal symptoms from the beginning of treatment; and (5) frequency of the second phase of the disease.

The inhibition of the hemagglutination test was performed by the standard technique, using tick-borne encephalitis virus as antigen and patient serum as a source of antibodies.[17] Ribonuclease activity in serum and in the cerebrospinal fluid was

Table 1.—RNAse Content in Serum and Cerebrospinal Fluid (CSF) of Patients With Tick-Borne Encephalitis

Subjects	RNAse Concentration* Serum	CSF	CSF/Blood Serum
Healthy (n = 79)	0.524 ± 0.019	...	...
Control group 1 (n = 20)†	0.536 ± 0.087	0.118 ± 0.0018	0.22 ± 0.0072
group 2 (n = 25)‡	0.621 ± 0.004	...	...
Patients with tick-borne encephalitis Acute periods Mild (n = 35)	1.094 ± 0.021	0.244 ± 0.01	0.22 ± 0.009
Meningeal (n = 52)	0.981 ± 0.016	0.248 ± 0.008	0.26 ± 0.007
Involvement of meninges and brain tissue (n = 21)	0.850 ± 0.014	0.242 ± 0.0011	0.29 ± 0.013
Early convalescence (20 to 25 days) Mild (n = 46)	0.582 ± 0.001	...	...
Meningeal (n = 51)	0.577 ± 0.005	...	...
Involvement of meninges and brain tissue (n = 23)	0.591 ± 0.009	...	...
Patients with tick-borne encephalitis, mild form (acute period) under RNAse treatment (n = 15)	2.635 ± 0.161	0.580 ± 0.068	0.22 ± 0.069

*Expressed in micrograms of pancreatic RNAse per milliliter of serum or cerebrospinal fluid with conditional activity 7 × 10^6 units/gm.

†Includes patients with radicular syndrome in osteochondrosis.

‡Patients with active form of osteoarticular tuberculosis accompanied by febrility.

Table 2.—Effects of Treatment on Symptoms in Patients With Tick-Borne Encephalitis, Mild Forms

Symptoms	Area of Clinical Trials*	Gamma Globulin No. of Patients	Gamma Globulin Duration, Days	RNAse No. of Patients	RNAse Duration, Days	P
Febrile period	N	60	5.5 ± 0.23	69	3.3 ± 0.3	0.001
	Kh	34	7.9 ± 0.09	19	4.0 ± 0.1	0.001
	K	2	6.4 ± 1.12	...	...	...
	S	12	7.0 ± 0.94	14	4.5 ± 0.66	0.05
Normalization of temperature from beginning of treatment	N	60	3.6 ± 0.2	69	1.7 ± 0.11	0.001
	Kh	34	4.4 ± 0.06	19	2.2 ± 0.09	0.001
	K	2	4.0 ± 1.03	...	...	...
	S	12	4.8 ± 0.97	14	2.2 ± 0.52	0.05
Time required for disappearance of meningeal symptoms from beginning of treatment	N	12	2.57 ± 0.94	18	2.2 ± 0.3	0.1
	Kh	...	...	...	...	...
	K	...	...	...	...	...
	S	4	11.0 ± 3.29	3	4.0 ± 0.38	0.05
Drop in body temperature during first day of treatment	N	60	0.27 ± 0.08	69	1.3 ± 0.11	0.001
	Kh	34	0.6 ± 0.02	19	1.2 ± 0.06	0.001
	K	2	0.5 ± 0.28	...	...	...
	S	12	0.3 ± 0.15	14	0.9 ± 0.23	0.05

*N indicates Novosibirsk district of West Siberia; Kh, Khabarovsk district (Far East); K, Kemerovsk district (West Siberia); S, Sverdlovsk district (Ural).

Table 3.—Effects of Treatment on Symptoms in Patients With Tick-Borne Encephalitis, Meningeal Form

		Gamma Globulin		RNAse		
Symptoms	Area of Clinical Trials*	No. of Patients	Duration, Days	No. of Patients	Duration, Days	*P*
Febrile period	N	52	7.4 ± 0.34	52	4.7 ± 0.27	0.001
	Kh	30	11.2 ± 0.03	18	6.3 ± 0.14	0.001
	K	8	11.0 ± 0.96	6	5.6 ± 0.49	0.1
	S	13	9.2 ± 0.93	8	5.5 ± 0.68	0.01
Normalization of temperature from beginning of treatment	N	52	5.3 ± 0.32	51	2.4 ± 0.21	0.001
	Kh	30	7.2 ± 0.13	18	3.0 ± 0.07	0.001
	K	8	5.6 ± 0.94	6	3.7 ± 0.61	0.1
	S	13	6.4 ± 0.64	8	3.5 ± 0.65	0.01
Time required for disappearance of meningeal symptoms from beginning of treatment	N	52	8.9 ± 0.61	52	4.7 ± 0.29	0.001
	Kh	30	18.7 ± 0.17	18	11.7 ± 0.34	0.02
	K	8	21.0 ± 1.27	6	15.6 ± 2.81	0.1
	S	13	18.9 ± 1.94	8	14.3 ± 1.01	0.05
Drop in body temperature during first day of treatment	N	52	0.33 ± 0.10	52	1.13 ± 0.12	0.001
	Kh	30	0.30 ± 0.002	18	1.20 ± 0.06	0.02
	K	8	0.24 ± 0.9	6	1.20 ± 0.25	0.1
	S	13	0.10 ± 0.25	8	1.00 ± 0.25	0.05

*Abbreviations as in Table 2.

Table 4.—Effects of Treatment on Symptoms in Patients With Tick-Borne Encephalitis With Involvement of Meninges and Brain Tissue

		Gamma Globulin		RNAse		
Symptoms	Area of Clinical Trials*	No. of Patients	Duration, Days	No. of Patients	Duration, Days	*P*
Febrile period	N	21	5.9 ± 0.58	16	2.2 ± 0.34	0.001
	Kh	26	14.5 ± 0.33	42	8.9 ± 0.12	0.001
	S	3	12.7 ± 0.88	1	5.0	...
Normalization of temperature from beginning of treatment	N	21	5.9 ± 0.58	16	2.2 ± 0.34	0.001
	Kh	26	7.9 ± 0.23	42	4.4 ± 0.08	0.001
	S	3	8.7 ± 0.99	1	2.0	...
Time required for disappearance of meningeal symptoms from beginning of treatment	N	21	10.4 ± 1.19	16	5.6 ± 0.94	0.01
	Kh	26	21.9 ± 0.79	42	16.6 ± 0.24	0.001
	S	3	23.7 ± 0.88	1	13.0	...
Drop in body temperature during first day of treatment	N	21	0.39 ± 0.17	16	0.90 ± 0.22	0.01
	Kh	26	0.10 ± 0.03	42	0.80 ± 0.02	0.001
	S	3	0.40 ± 0.20	1	1.4	...

*Abbreviations as in Table 2.

assayed by the technique of Schneider and Hogebum as modified by Belousova,[18] and expressed in micrograms of pancreatic RNAse with conditional activity 7 × 10^6 units/gm.

RESULTS

Preliminary studies were performed to establish the optimal doses of RNAse. It was concluded that most efficient method of treatment with RNAse should ensure a continuously elevated RNAse blood level throughout the period of treatment. After a single intramuscular administration of 30 mg of RNAse, its content in serum reached peak values in two hours. In three to four hours, RNAse content began to decrease, reaching the initial level by seven to eight hours (Fig 1). When 45 mg of RNAse were injected every six hours, there were sharp fluctuations of RNAse content in blood (Fig 2). Administration of 30 mg of RNAse every four hours provided stable high concentrations of the enzyme that exceeded normal values by two to three times (Fig 3).

The initial RNAse activity in serum and cerebrospinal fluid was determined in patients and in healthy subjects (Table 1). In patients with tick-borne encephalitis, the RNAse level turned out to be higher than in normal healthy subjects or in patients with nonviral diseases (radicular syndrome in osteochondrosis and active form of osteoarticular tuberculosis). The possible protective significance of this rise will be discussed below.

The samples of serum and cerebrospinal fluid were taken from healthy subjects and patients between eight and nine o'clock in the morning, before breakfast. They were taken from patients with tick-borne encephalitis in the acute periods on the first day of admission to hospital, before

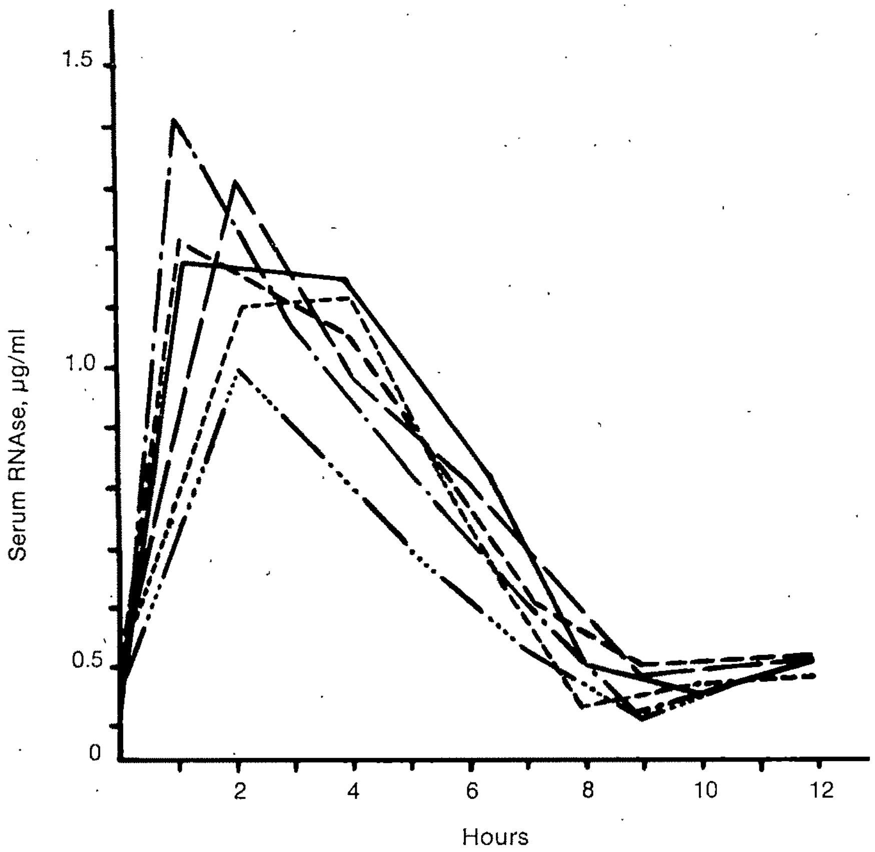

Fig 1.—Changes in serum content of RNAse in healthy subjects after a single intramuscular injection (30 mg).

Table 5.—Titers of Antibodies Against Tick-Borne Encephalitis Virus*

Day of Disease	Treatment	
	Gamma Globulin	RNAse
2	. . .	2.8 ± 0.3 (n = 11)
5	4.5 ± 0.73 (n = 8)	3.7 ± 0.58 (n = 21)
10	4.5 ± 0.56 (n = 11)	5.5 ± 0.49 (n = 18)
15	4.3 ± 0.47 (n = 13)	6.9 ± 0.33 (n = 18)
20	4.6 ± 0.51 (n = 15)	7.8 ± 0.45 (n = 11)
25	4.9 ± 0.32 (n = 8)	8.5 ± 0.49 (n = 5)

*Established by the inhibition of hemagglutination reaction in serum of patients treated by different methods.

the RNAse injection. In patients with tick-borne encephalitis in the early convalescent period, samples were taken 15 days after the RNAse injections were stopped, and in patients with tick-borne encephalitis of the mild form in the acute period, they were taken four hours after the sixth RNAse injection. Ribonuclease activity was assayed according to Golubev and Sinitsin,[17] and expressed in micrograms of pancreatic RNAse per milliliter of serum enzyme with the activity 7 × 10^6 units/gm.

After the intramuscular administration of RNAse, its content in serum and cerebrospinal fluid increased by 2.4 times on the average (Table 1). This was taken to mean that RNAse is able to pass through the blood-brain barrier. The penetration coefficient determined as the ratio of cerebrospinal fluid RNAse concentration to its concentration in serum made up 0.22 to 0.23 in patients with the mild form of tick-borne encephalitis both before and after RNAse administration, and was the same in patients with nonviral diseases. The penetration coefficient rose with the severity of the diseases, and in patients with the meningeal form and forms involving brain tissue, attained values of 0.26 ± 0.007 (n = 50) and 0.29 ± 0.013 (n = 21), respectively.

The comparison of treatment of patients with tick-borne encephalitis with RNAse and antiencephalitic gamma globulin has demonstrated the considerable advantages of the former (Table 2 through 4). Under RNAse treatment the febrile period was shorter, the temperature normalized twice as quickly, and there was a rapid improvement in the patient's general condition as muscular pains disappeared, nausea and vomiting stopped, and appetite reappeared. Under the influence of RNAse the temperature for the first 24 hours of treatment dropped 0.9 to 1.4 C, while in patients treated with gamma globulin temperatures dropped only 0.27 to 0.6 C. In RNAse-treated patients meningeal symptoms regressed promptly and cells in cerebrospinal fluid rapidly returned to normal. Of 29 RNAse-treated patients, 18 had a normal cell composition of the cerebrospinal fluid 15 days after the beginning of the disease, while in 20 gamma globulin-treated patients only five had a normal cell composition by the 15th day. A biphasic course of the disease characterized the mild forms of tick-borne encephalitis. Of 69 gamma globulin-treated patients with mild forms, nine had a biphasic course of the disease. In 102 RNAse-treated patients with this form, the biphasic course of the disease was observed in none. Prolonged asthenia was often observed after gamma globulin treatment, and much more seldom in RNAse-treated patients.

Noteworthy are the results of RNAse treatment in patients with focal brain lesions. A high mortality and morbidity is associated with this form, especially in the Far East. In Khabarovsk clinics, about half of these patients treated with gamma globulin died, and only about 20% died when treated with RNAse. The percentage of paralysis was 30% and 7% of clinical cases, respectively.[19] Gamma globulin treatment was associated with complications in 9% of the cases. In 246 RNAse-treated patients there were no adverse reactions or aftereffects.

Passive immunization is known to

inhibit immunogenesis. In fact, when antiencephalitic gamma globulin is administered, the amount of antiviral antibodies increase for 15 days after the beginning of the disease, and goes up only slightly by the 20th to the 25th day. In RNAse treatment, as in treatment with symptomatic remedies, there is no inhibition of immunogenesis, and the hemagglutinin titers increase from the first days of the disease (Table 5).

COMMENT

The data show that the therapeutic effect of RNAse in tick-borne encephalitis is considerably higher than that of gamma globulin, which still remains the only specific remedy for relief of this disease. The targets of these two remedies are different: gamma globulin interacts with viral proteins and thus neutralizes the viruses outside the cell; RNAse seems to act only on viral RNA when the virus is multiplying within the cell, and on viral RNA if it appears outside the cell. Alterations of the antigen pattern of the virus, as a result of mutation for instance, may attenuate the antiviral effect of a specific gamma globulin. This is inconsequential for RNAse, as it acts on the phosphodiesteric bonds of viral RNA molecules.

Ribonuclease administration does not produce any allergic reactions, and this seems to be connected with the fact that this enzyme is a protein of relatively low molecular weight (13,000) and a weak antigenic activity.

Cells capture exogenous proteins (including RNAse) and most viruses by means of pinocytosis.[1,2] Probably, that is the way nucleases and viruses find themselves in the same cell space in vesicles or vacuoles, thereby ensuring the degradation of viral nucleic acids and isolation of the enzyme from RNAse-sensitive cell structures. In addition, most cell RNA forms complexes with proteins that seem to reduce their susceptibility to RNAse. Perhaps that is why antiviral concentrations of RNAse do not damage cell structures and are devoid of toxic effect.[15]

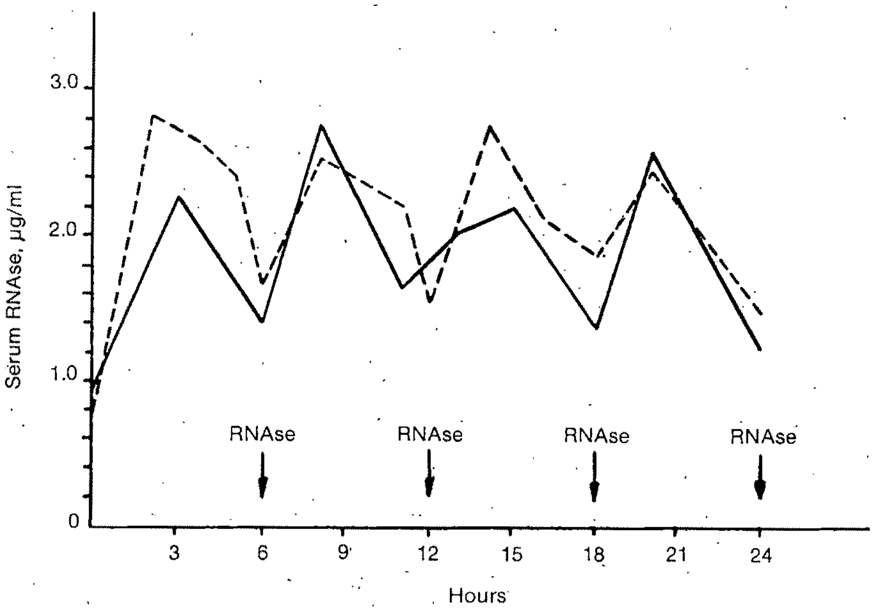

Fig 2.—Changes in serum content of RNAse in patients with encephalitis when 45 mg of enzyme was injected every six hours.

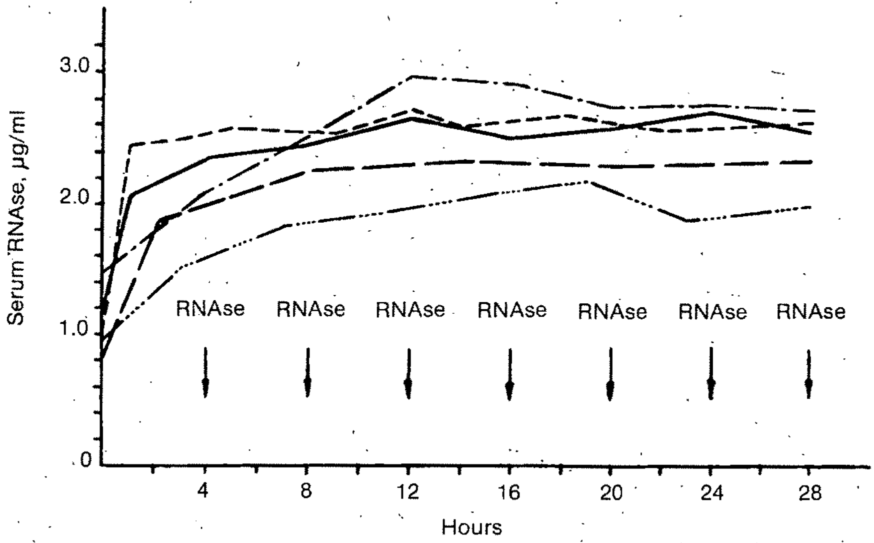

Fig 3.—Changes in serum content of RNAse in patients with encephalitis when 30 mg of enzyme was injected every four hours.

In patients with tick-borne encephalitis serum RNAse content is higher than in healthy subjects and in patients with nonviral nervous diseases. One can suppose that RNAse of the internal milieu and cells of the organism serve as a natural means of antiviral defense, and that the increase in the activity or content of these enzymes under infection with RNA-containing viruses may be a defensive reaction.

Studies of RNAse activity in cerebrospinal fluid of patients with different nervous diseases[20,21] have shown that in poliomyelitis, RNAse activity is much higher than in other nonviral diseases (meningitis, neurosyphilis, brain tumors, epilepsy). Increases in RNAse activity in cerebrospinal fluid was also found in patients with serous meningitis provoked by the coxsackie virus.[22] It was established that RNAse activity increases in brain tissue of mice infected with the Japanese encephalitis virus.[23] Thus the administration of exogenous RNAse in viral diseases may serve as a reasonable means of enhancing the natural mechanism of antiviral defense.

Our data confirm the well-known fact that passive immunization treatment with antiencephalitic gamma globulin inhibits immunogenesis. On the contrary, RNAse treatment, judging from the hemagglutination inhibition data, does not block formation of antibodies against tick-borne encephalitis virus (Table 5). Probably the amount of viral proteins formed during the early acute phase of the disease is sufficient to induce antibody formation in spite of the subsequent inhibition of the multiplication of the viruses under the action of RNAse. Therefore immunological defense can support the beneficial effect of RNAse.

On the grounds of these reported clinical results, RNAse was recently introduced in this country officially as a new antiviral drug for the efficient treatment of tick-borne encephalitis.

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Seizures and Adaptive Abilities

A Case of Identical Twins

Carl B. Dodrill, PhD, Allan S. Troupin, MD

• The effects of seizures on performance were investigated in a pair of identical twins who were concordant for incidence of epilepsy, but who had highly contrasting histories of seizure frequency. An evaluation of abilities focused on intelligence, academic achievement, neuropsychologic functions, and emotional and social adjustment. While both twins showed some disabilities, the twin with the larger number of seizures was less able in every area examined. The results suggest that the greater seizure frequency is related to the lesser abilities.

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Studies of disease in monozygotic twins provide individuals with identical genetic makeups, but who may differ with respect to the disorders under investigation. Such studies in epileptics have suggested that febrile convulsions have a moderately adverse impact on functioning in later life[1] and that intellectual abilities may be less among twins who have more severe seizure disorders than their counterparts.[2,3] However, these studies have evaluated psychological functioning almost entirely in the area of "intelligence" and often have utilized data collected in an incidental fashion. This investigation evaluated the psychological effects of a notable difference in seizure frequency in a pair of monozygotic twins where that difference was the only discernible one between them. Psychological assessment included not only intellectual abilities, but a broad range of neuropsychological, emotional, and social abilities as well.

SUBJECTS AND METHODS

The twins are right-handed, monozygotic girls, and were the product of an uncomplicated 8½-month pregnancy. Two previous pregnancies had resulted in normal children. Each twin was delivered from a breech presentation, but without complications or the use of forceps. A single placenta was also delivered without complication. Twin 1 preceded twin 2 by 20 minutes, and each twin weighed 2.2 kg. Both were placed in oxygen for some hours because of their weight, but not because of clinical distress. Both developed normally and equally until the onset of seizures. They sat at six months, walked alone at 14 months, and spoke "twin talk" until approximately 24 months, when they spoke sentences effectively and with equal fluency. Family history showed seizures in the paternal grandmother, a paternal cousin, and a maternal uncle.

Twin 1

This child began having grand mal and petit mal seizures at age 6. These seizures were brought under control by age 8 with the use of mephobarbital, phenytoin sodium, ethosuximide, and trimethadione. However, difficulty with the seizures and side effects of her medication were associated with a poor performance in school, and she repeated the first year. At age 8, the mephobarbital and trimethadione were stopped with improvement in school performance and without the return of seizures. At this time, she was believed to be functioning less well in school than her twin sister, although both were considered to be developing normally and performing as average students. When she was 12 years old, the ethosuximide was discontinued slowly, but the petit mal seizures recurred; the medication was restarted with success. Except for single grand mal seizures at ages 18 and 19, she has remained seizure-free since that time. Her lifetime total of major motor seizures is seven. At age 18, phenytoin was replaced by primidone because of gingival hypertrophy. When first seen at the University of Washington Seizure Clinic at age 19, she was using primidone, 750 mg/day, and ethosuximide, 500 mg/day.

At age 5, six months prior to the onset of seizures, the patient had an electroencephalogram performed because of the onset of seizures in her twin sister. The EEG was abnormal and paroxysmal because of polyspike waves precipitated by photic stimulation. No clinical phenomena were apparent. One year later and after the onset of seizures, her EEG showed notable generalized polyspike wave abnormalities, but without either clinical phenomena or activation by photic stimulation. Her EEG

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at age 9 was only mildly paroxysmal with similar abnormalities that were photically stimulated. The EEG performed at age 19 was normal.

Complete neurologic examinations throughout her course were normal with the exception of scattered signs of anticonvulsant side effects during childhood. At age 19, the examination showed her to be a pleasant, normally developed young woman without neurologic abnormalities. Serum analysis showed a primidone level of 7.6μg/ml, a phenobarbital level of 11.6μg/ml, and an ethosuximide level of 56μg/ml.

Twin 2

This child began having seizures at age 5, ten months prior to the onset in her sister. Her first seizure was a nonfocal grand mal seizure and subsequently flurries of classical petit mal seizures developed. Initially, she was treated with a mixture of small doses of various anticonvulsant drugs without much improvement and with considerable intoxication. At age 6, following several grand mal seizures, she was placed on phenytoin, mephobarbital, and ethosuximide with gradual improvement in seizure control. A first attempt to remove the mephobarbital led to a return of grand mal seizures, but when the mephobarbital was discontinued at age 8, she was seizure-free for three years. At age 11, however, both grand mal and petit mal seizures returned. Since then she has averaged three to four grand mal seizures each year for a lifetime total of 37. She continued to have several petit mal seizures each week. The parents reported that this twin has always had more seizures than twin 1, even when twin 1 was having her largest number of attacks. Menarche was at age 13. As she progressed in school, her academic performance began to fade. Despite her repeating the first grade, by the age of 12 she was being promoted because of age rather than achievement. Eventually, she was placed in a vocational rather than an academic program. Except for the addition of phenobarbital during puberty in twin 2, the anticonvulsant programs have been nearly identical for the twins. At age 17, primidone was substituted for phenytoin because of gingival hypertrophy.

Her initial EEG at age 6 showed widespread synchronous polyspike wave discharges, but five months later when good seizure control had been established, her EEG was normal. An EEG at age 8 showed moderate generalized polyspike wave discharges with additional activation by photic stimulation. Six years later, the tracing was similar, but did not show sensitivity to photic stimulation. The EEG at age 19 showed frequent generalized polyspike wave activity without clinical phenomena and without activation by photic stimulation. Her EEGs, very similar to those of her sister through age 9, retained these same generalized paroxysmal abnormalities beyond that time in keeping with her persisting clinical seizures.

The neurologic examinations when the patient was a child were normal with the exception of occasional signs of anticonvulsant side effects. By age 13, she was noted to be mentally slow, and this has become gradually more prominent. At age 15, the Wechsler Intelligence Scale for Children (WISC) resulted in a verbal intelligence quotient (IQ) of 67, a performance IQ of 54, and a full-scale IQ of 57. There have never been signs of somatic neurologic impairment, although signs of anticonvulsant side effects have appeared intermittently. In April 1975, her neurologic examination was normal, and she looked much like her twin sister except for mental slowing. At that time, she was using ethosuximide (750 mg/day), primidone (750 mg/day), and phenobarbital (150 mg/day). While the serum level for ethosuximide was not obtained, the levels for the other two drugs were 9.6μg/ml and 80.4μg/ml respectively.

Description of Test Battery

Tests in four areas were individually administered to each twin, neither of which was either ictal or postictal at the time of testing.

Intelligence.—The Wechsler Adult Intelligence Scale (WAIS) assessed verbal and performance abilities.

Academic Achievement.—The Wide-Range Achievement Test (WRAT)[4] provided grade equivalent and percentile scores for the areas of reading, spelling, and arithmetic.

Neuropsychological Functions.—A battery of tests was selected which most prominently included Halstead Neuropsychological Test Battery for Adults.[5] This battery consisted of the Category Test (a test of complex concept formation and abstraction abilities), the Tactual Performance Test (TPT, a complex procedure involving motor coordination, tactile form discrimination, problem solving, and incidental memory), the Seashore Rhythm Test (a test requiring sustained attention and concentration as well as the ability to remember and compare rhythmic sequences), the Speech Sounds Perception Test (a test requiring the accurate perception of spoken stimulus sound through hearing and its relation to visually presented language symbols), and the Tapping Test (a relatively pure test of motor speed employing the index finger of each hand). Other neuropsychological tests included the Trail-Making Test (a psychomotor test requiring flexibility in thinking and in the use of language symbols), Reitan's revision of the Halstead-Wepman Aphasia Screening Test (a test that surveys a variety of language-related deficits), the Reitan-Kløve Sensory-Perceptual Examination (including tests of unilateral and bilateral simultaneous tactile, auditory, and visual stimulation as well as tests of finger agnosia, agraphagnosia, and astereognosis), and the Seashore Tonal Memory Test (a test requiring sustained attention and concentration as well as the ability to remember sequences of tones).

Emotional and Social Adjustment.—To survey emotional status, the Minnesota Multiphasic Personality Inventory (MMPI) was administered. To assess self-perceived social functioning capabilities, the Heimler Scale of Social Functioning[6] was administered. This instrument quantifies satisfactions in important areas of life, signs of frustration and difficulties, and degree of optimism in general outlook toward life.

Finally, to provide information on the relationship of the parents' abilities to the twins, a short, timed test of mental ability (Wonderlic Personnel Test, form A[7]) was administered to all four family members.

RESULTS

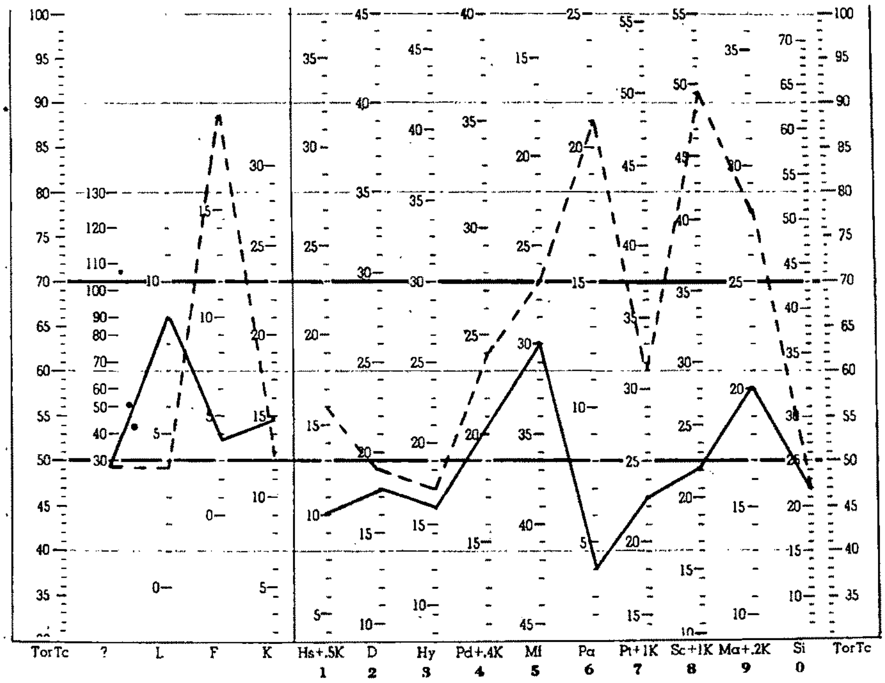
The summary results on the WAIS are presented in the Table. On nine of the 11 subtests, twin 1 did better than twin 2, and in the other two instances, they earned identical scaled scores. While the overall performance of twin 1 fell into the dull normal range at about the 18th percentile in comparison with other individuals her age, that of twin 2 fell in the range of mild mental retardation and at about the first percentile. This contrast was found for both the verbal and performance areas.

In the area of academic achievement, both girls performed substantially below average, particularly considering that they had nearly completed the twelfth grade. Yet a contrast between their performances favored twin 1 in each of the three academic areas assessed.

Performance by the twins on the neuropsychological measures is also presented in the Table. Twin 1 performed better than twin 2 in each instance. While twin 1's performance was in the range of moderate impairment of adaptive abilities dependent

Comparison of Twins 1 and 2 on Various Psychological Measures

Measure	Twin 1	Twin 2
Wechsler Adult Intelligence Scale		
Verbal IQ	92	68
Performance IQ	81	64
Full-scale IQ	86	64
Wide-Range Achievement Test		
Reading achievement, No. of errors	96	98
Spelling achievement, min	18.2 (all 30 in)	45.0 (5 in)
Arithmetic achievement, No. remembered	6	5
Category Test, No. localized	4	2
Tactual Performance Test		
Time, No. correct	23	17
Memory, No. of errors	7	14
Local, No./10 sec	42	31
Seashore Rhythm Test, %	71	100
Speech-Sounds Perception Test, sec	22	90
Finger tapping, dominant hand, sec	61	313
Percentage of impaired scores, No. of errors	19	38
Trail-Making Test		
Part A, No. correct	26	8
Part B, grade	7.5	5.4
Sensory-Perceptual Examination, grade	7.0	4.0
Seashore Tonal Memory, grade	6.5	2.3
Heimler Scale of Social Functioning		
Satisfactions	92	60
Frustrations	14	52
Optimism in outlook	78	81



Minnesota Multiphasic Personality Inventory profiles for twin 1 (solid line) and twin 2 (broken line). (Profile form copyright 1948 by the Psychological Corporation.)

on the integrity of brain functions, twin 2's performance was in the range of severe impairment. The difference between the twins was most striking on psychomotor problem solving tasks such as the TPT in which twin 2 took much longer to place fewer blocks in the formboard while deprived of visual cues. Other contrasts between their performances included more difficulty in dealing with language symbols and spatial relationships by twin 2. The total pattern of test results was such as to suggest impaired functions of both cerebral hemispheres for both twins, but much more so for twin 2.

On the Heimler Scale of Social Functioning, twin 1 reported more satisfactions than twin 2, while at the same time reporting fewer signs of frustrations or difficulties. A more detailed examination of the profiles showed that twin 1 reported satisfaction in all areas assessed, but twin 2 reported minimal satisfaction in the peer relationship and school adjustment areas. While twin 1 showed only scattered signs of frustrations and difficulties, twin 2 showed strong clusterings of such signs on questions relating to depression and feelings of persecution. The contrasts on this instrument make it appear that twin 1 has a substantially better personal adjustment. The attitude of optimism portrayed by twin 2 may be superficial and primarily an attempt at holding herself together despite her difficulties.

The MMPI profiles of the twins (Figure) are in substantial contrast to one another. While both were valid,[8] there was some suggestion that twin 2 may not have been able to read and understand at least some of the test items. For example, she endorsed several items that are often endorsed by individuals having frank hallucinations and delusions, and the profile she rendered was not unlike that commonly seen in paranoid schizophrenia. While we have seen no clinical evidence for such a disorder, it does not appear possible to dismiss all her deviant responses, and the adequacy of her emotional adjustment is called into question. Twin 1's profile, on the other hand, falls well within normal limits.

The Wonderlic Personnel Test rendered IQ estimates for the father, mother, twin 1, and twin 2 of 110, 96, 89, and 72, respectively. Thus, it appeared that both twins were functioning below the level of the parents. Although the intellectual levels of the twins before the onset of seizures was not known, the presence of a seizure disorder (and particularly an active one) was associated with poorer performance.

COMMENT

The twins examined in this study provide suggestive evidence about the effects of seizures themselves on performance, since the one factor clearly differentiating them was their contrasting seizure frequency. We would stress that prior to the onset of seizures, neither parent had any impression that one twin was intellectually more capable than the other, or in fact that there were any differences between the twins whatever. On the contrary, they had difficulty in telling the twins apart, and it has only been in more recent years that this discrimination has been easier. On our examination, the twins appeared similar, but twin 2 seemed to be duller and to have a flattened affect. The difference was enough to tell them apart easily.

There has been vigorous support for both sides of the argument that seizures damage the brain. It seems likely that many seizure patients are not affected this way.[9] On the other hand, many institutions have at least some patients who were ostensibly normal as late as puberty before the onset of seizures and without other neurologic disease. There is no current evidence to explain why this happens to some people and not to others, but there is now some experimental documentation of the fact that this phenomenon does exist. Harris[10] has shown that there is distant neuronal degeneration in experimental focal epilepsy. The works of Wasterlain and Plum[11-13] have demonstrated the inhibitory effect of seizures on brain protein synthesis and brain growth, and eventually on behavioral development in experimental animals. Such studies are obviously not possible in humans. Our study of monozygotic twins with similar seizure patterns, EEGs, ages at onset, and absence of other neurologic disease perhaps provides observations as close to a controlled experiment as possible. Further, we would note that neither twin has experienced status epilepticus so that the intellectual deterioration often attributed to that condition[14] may not be given as explanation for twin 2's poor performance.

The contrast between the two women on the wide variety of measures of adaptive ability was striking, and we could only conclude that twin 2 was considerably less able to cope with problems in everyday life than was twin 1. The EEG and developmental similarities do not support the contention that twin 2 had a more seriously damaged brain initially and thus that the seizures and the performance are merely reflections of this. We believe that the difference in seizure frequency is the primary variable to be related to this notable difference in adaptive abilities. However, we also recognize that factors may have been in operation of which we are not aware.

We favor a rather aggressive and logically formulated program of seizure control and would speculate that such an approach might have been helpful in controlling twin 2's seizures and in permitting more normal development. We have found that substantial doses of fewer and more specifically directed anticonvulsants can be employed without causing adverse effects to adjustive abilities.[15] When used in this fashion, we believe that drugs are less dangerous to development than seizures, and we would underscore the critical importance of controlling the latter during the developmental years.

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Nonproprietary Name and Trademark of Drug

Ethosuximide—*Zarontin*.

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Effects of Nerve Stimulation on Human Muscle

Theodore L. Munsat, MD; Donald McNeal, PhD; Robert Waters, MD

• A phasic program of femoral nerve stimulation was used to reduce refractory knee flexion contractures in five patients. In one, rectus femoris was tenotomized before starting stimulation to reduce hip flexion contracture. Muscle biopsies were performed before and after 5 to 12 weeks of intermittent stimulation at separated sites on the same muscle. In the four patients where muscle contraction was isometric, type I fibers increased 3.7%, 6.4%, 48.4%, and 30.4%, respectively. Both fiber types in each patient showed an increase in size ($P < .001$). In the tenotomized muscle, where contraction was isotonic at a shortened length, the proportion of type I fibers decreased from 40.2% to 25.4%, and their mean diameter also decreased ($P < .001$). These observations suggest that the physical conditions of contraction may be more important than the pattern of neuronal discharge in determining the metabolic profile of human muscle fibers.

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Recent years have seen an increasing interest in the factors that determine the biochemical and physiological characteristics of skeletal muscle. Of particular interest has been the question of nerve-muscle interaction.[1,2] Several experimental approaches have been utilized to study this relationship that are not applicable to man, necessitating extrapolation from animal studies in attempting to understand human motor unit function. Species differences,[3] however, make this extrapolation somewhat hazardous.

During the past several years, a program evaluating the therapeutic benefit of prolonged peripheral nerve stimulation with implanted electrodes in man has been underway at Rancho Los Amigos Hospital-University of Southern California.[4-6] This has provided an opportunity, by performing skeletal muscle biopsies before and after varying periods of stimulation, to evaluate myofiber changes. The program was initially utilized in an effort to correct the foot-drop and hip extensor weakness of stroke patients. It was found to be safe and well tolerated. More recently, implanted electrodes have been used to stimulate the femoral nerve to reduce intractable knee flexion contractures. In effect, the force of the quadriceps muscle is used to fully extend the knee when other therapeutic approaches prove inadequate. This article records observations of myofiber changes in five patients who received femoral nerve stimulation for 5 to 12 weeks. In one, rectus femoris was surgically released to reduce severe hip flexion contracture, giving us an opportunity to study tenotomized muscle stimulated in a similar manner. One patient, in our preliminary report on this project,[6] sustained partial femoral nerve injury at the time of electrode implacement. His findings have been replaced by those of a more recent subject (patient 2) in this report.

METHODS

The stimulation system consisted of a bedside, radio-frequency transmitter, transmitting antenna, and subcutaneous receiving antenna that was connected to a bipolar, tinsel wire, platinum electrode embedded in silicone and wrapped about the femoral nerve.[7] The stimulus was a surged, rectangular pulse, with a pulse duration of 0.2 msec at 33 Hz. Voltage was adjusted for patient acceptance; roughly 50% of maximum tetanic contraction. After healing of the incisions and a build-up period of one to two weeks, stimulation

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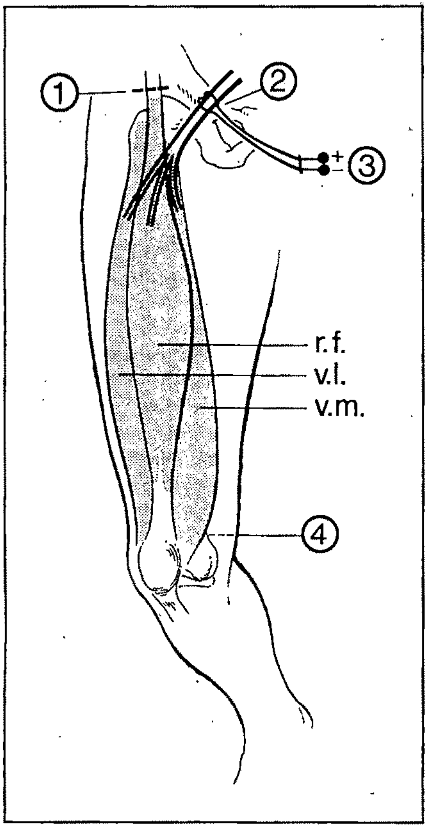


Fig 1.—Pertinent structures involved in stimulation system: (1) site of rectus femoris tenotomy in patient 5 only; (2) bipolar electrode wrapped about femoral nerve; (3) battery-operated power unit at bedside; and (4) surgical release of hamstring muscles performed prior to nerve implant. Rectus femoris (rf); vastus lateralis (vl); vastus medialis (vm).

Table 1.—Change in Fiber Type Proportion With Femoral Nerve Stimulation

Patient	Diagnosis	Stimulation Period, wk	% Type I Before	% Type I After	% Change	P
1	Tuberculous meningitis with myelopathy	12	40.6	44.3	+3.7	<.05
2	Atherosclerotic cerebrovascular disease	12	23.8	30.2	+6.4	<.05
3	Head trauma	5	29.6	78.0	+48.4	<.001
4	Subarachnoid hematoma, 2° basilar artery aneurysm	10	8.6	39.0	+30.4	<.001
5*	Cerebrovascular disease	12	40.2	25.4	−14.8	<.001

*Muscle tenotomized before stimulation.

Table 2.—Increase in Mean Fiber Diameter With Femoral Nerve Stimulation

Patient	Fiber Diameter, μ			P
	Before	After	Change	
		Type I		
1*	25.4	52.0	+26.6	<.001
2	34.1 ± 7.4	40.6 ± 10.6	+6.5	<.001
3	26.2 ± 5.3	49.6 ± 15.4	+23.4	<.001
4	37.0 ± 7.7	72.4 ± 12.3	+35.4	<.001
5†	38.9 ± 12.4	32.5 ± 8.4	−6.4	<.001
		Type II		
1*	17.2	27.7	+10.5	<.001
2	12.4 ± 4.3	32.9 ± 8.4	+20.5	<.001
3‡	27.1 ± 7.8	56.2 ± 7.3‡	+29.1	<.001
4	20.8 ± 8.8	86.2 ± 18.1	+65.4	<.001
5†	32.4 ± 12.8	34.6 ± 7.8	+2.2	<.01

*Because of wide scatter of poststimulation values, a log transformation was performed, and values are expressed as geometric means. Other values expressed as mean ± SD.

‡The poststimulation figure for type II fibers represents only those fibers greater than 40μ.

†Muscle tenotomized prior to stimulation.

Table 3.—Effects of Femoral Nerve Stimulation on Oxidative (NADH-TR) Activity of Muscle Fibers

	% Total Fiber Count					
	Dark		Intermediate		Light	
Patient	Prestimulation	Poststimulation	Prestimulation	Poststimulation	Prestimulation	Poststimulation
2*	38.9	36.9	...	...	61.1	63.1
3	38.2	70.5	32.2	14.8	29.6	14.7
4	26.9	40.9	47.9	39.0	25.2	20.1
5*	33.1	6.0	...	...	66.9	94.0

*Only two intensities of staining observed.

was carried out for one-hour epochs out of every four hours around the clock. During the one-hour stimulation period, the stimulus was alternately on for five seconds and off for 25 seconds. This program approximates, in frequency and pattern, a phasic discharge.[8-10] Since knee extension was limited by contracture, the stimulated quadriceps was contracting isometrically. In patient 5, surgical release of rectus femoris, resulted in a muscle that contracted more isometrically when stimulated (Fig 1).

Muscle biopsies were carried out on superficial fascicles at separated sites of the same muscle (either vastus lateralis or rectus femoris) before and after stimulation. Care was taken to avoid musculotendinous junctions and damaging nerve or blood vessels. Muscle for histochemical study was immediately dusted with talc, quenched in liquid nitrogen, and stored at −70 C. Frozen tissue was embedded in medium and sectioned at 8μ to 10μ in a cryostat at −20 C. Reactions were carried out by minor modifications of established techniques as follows: hematoxylin-eosin,[11] modified Gomori trichrome,[12] oil red O for lipid,[13] reduced nicotinamide adenine dinucleotide-tetrazolium reductase (NADH-TR);[14] succinic dehydrogenase (SDH),[15] myofibrillar adenosine triphosphatase (ATPase) at pH 9.4 and 4.5,[16] PAS with and without diastase predigestion for glycogen,[11] and phosphorylase with and without adenosine monophosphate.[17]

Muscle fibers were classified type I if they reacted lightly with the alkaline myofibrillar ATPase reaction and type II if they reacted darkly.[18] No attempt was made to further subdivide type II fibers. Although direct studies in humans are lacking, physiologic speed and discharge pattern are correlated with the amount of alkaline myofibrillar ATPase activity.[19] Thus, for purposes of this discussion, the physiologic terms "fast" and "phasic" will be used to refer to fibers (units) with high

ATPase activity, or type II fibers. Conversely the terms "slow" and "tonic" will refer to fibers (units) with low ATPase activity or type I fibers. For estimation of "oxidative enzyme" activity, fibers were subjectively categorized into two or three intensities of reaction product with the NADH-TR reaction.

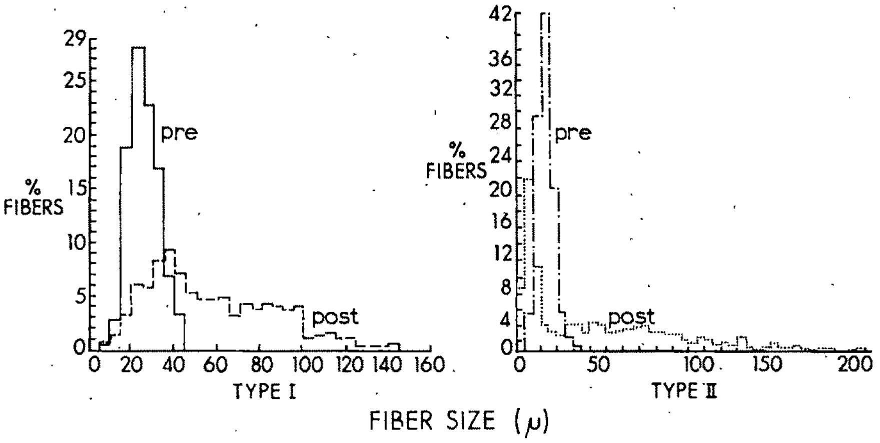
For fiber counts, a minimum of 200 fibers were measured and typed.[20] In several cases of well-preserved and well-stained tissue, all fibers in the biopsy specimen were counted. The Student *t* test was used to determine statistical significance between means. In patient 3, the poststimulation histogram showed a bimodal distribution for type II fibers, with a break at 40μ and mean diameters of 25.7μ ± 5.4 and 56.2μ ± 7.3, respectively. Since this suggested that one population of fibers was not sufficiently stimulated, only the second group, 40μ and larger, was used for statistical purposes.

All patients had severe, intractable flexion contractures of the lower extremity, associated with advanced bilateral upper motor neuron disease. The physical deformities were severe enough to justify surgical intervention. Femoral nerve stimulation was used after surgical release of the hamstrings was found to be not completely effective. Informed consent was obtained from the patient or, when he was deemed not fully competent, from a legal guardian. The protocol for this study was approved by the Human Research Committees of Rancho Los Amigos Hospital and Los Angeles County-University of Southern California Medical Center.

RESULTS

The clinical results were satisfactory and will be described in detail in a subsequent communication. We have been concerned with the safety of this therapeutic approach.[6] In brief, we have found that repeated stimulation of implanted nerves for as long as five years in remarkably safe, and although a build-up of endoneurial connective tissue does occur, axons and myelin sheaths are generally spared. Scattered axonal damage does occur, but this is minimal.

Table 1 lists the changes in fiber type proportion that occurred after femoral nerve stimulation. There was no relation between length of stimulation and degree of fiber type change. The greatest change (+48.4%) occurred in patient 3, who was stimulated for the shortest period (five weeks), while the least change



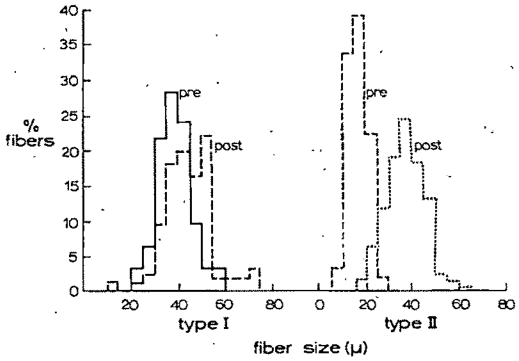
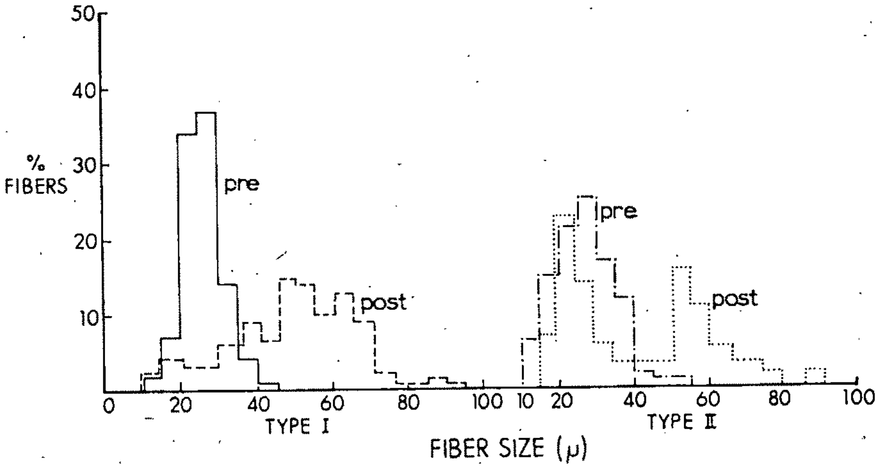
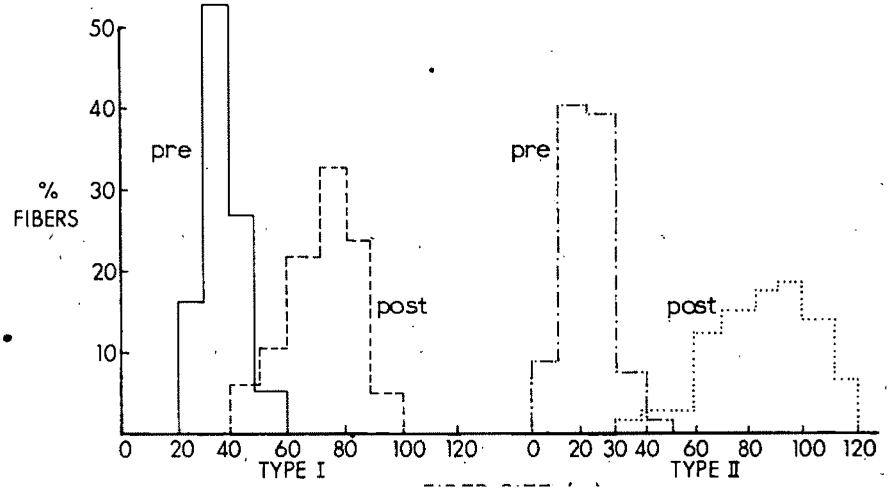


Fig 2.—Prestimulation and poststimulation histograms. All patients demonstrated type II atrophy prior to stimulation. Top, Patient 1 (12 weeks' stimulation). Poststimulation histogram shows large number of atrophic fibers, possibly related to overstimulation. Right, Patient 2 (12 weeks' stimulation). Poststimulation pattern normal. Below, Patient 3 (five weeks' stimulation). Biphasic poststimulation type II histogram suggests that only some of fibers in biopsy specimen were stimulated. Bottom, Patient 4 (ten weeks' stimulation). Poststimulation pattern normal.





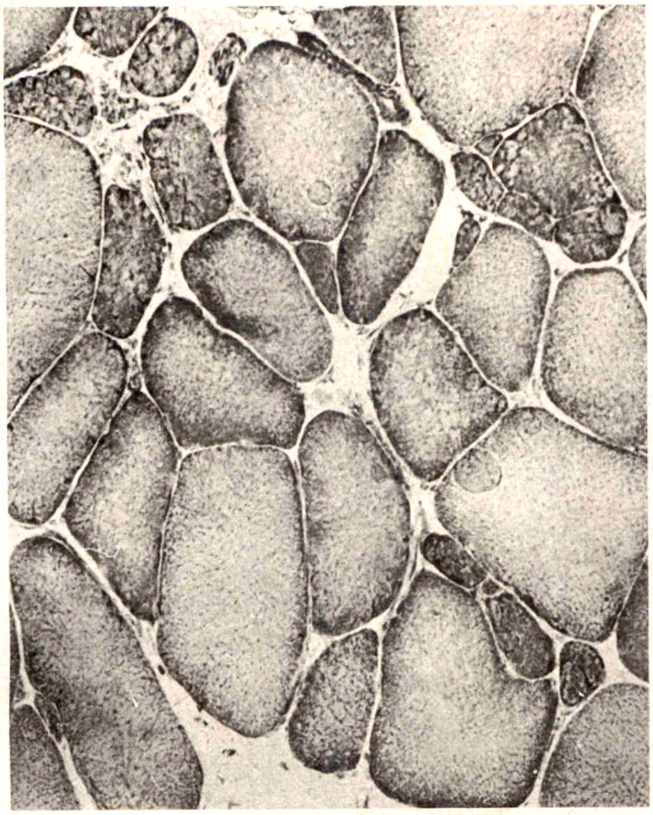


Fig 3.—Changes in oxidative enzyme activity possibly due to excessive stimulation (patient 1). Most of larger fibers have fairly normal pattern. Other fibers demonstrate aggregation and clumping as well as areas devoid of reaction product (NADH-TR, original magnification ×150).

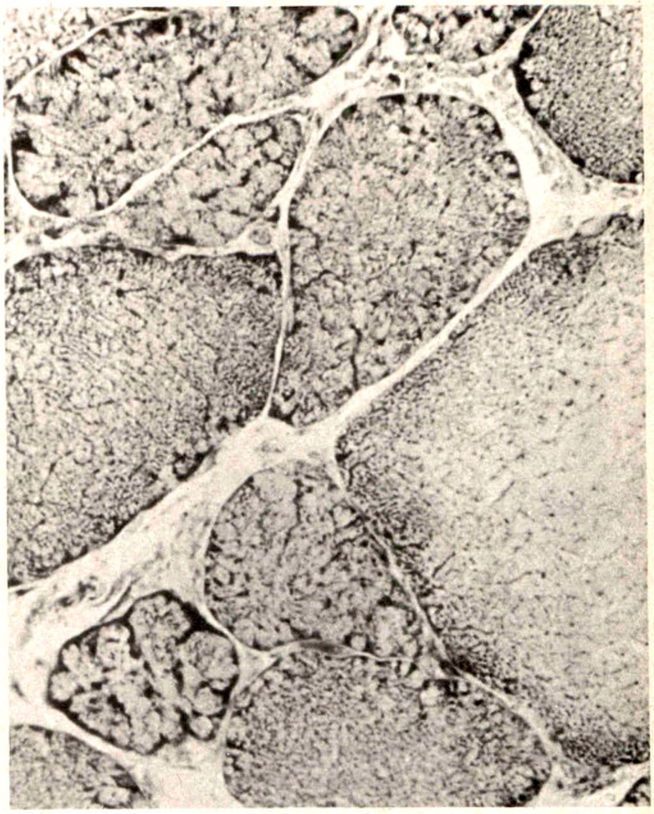


Fig 4.—Clumping of reaction production in smaller fibers (patient 1). (NADH-TR, original magnification ×384).

(+3.7%) occurred in patient 1, who was stimulated for the longest period (12 weeks). In all cases where the muscle was not tenotomized and was contracting isometrically, type I fibers increased in relative numbers, although a phasic program of stimulation was used. In the patient whose muscle was tenotomized before stimulation (patient 5), the change in fiber composition was in the reverse direction, with a 14.8% decrease in type I fibers ($P < .001$).

Fiber size measurements (Table 2) showed a significant ($P < .001$) increase in both fiber types in all patients where muscle was contracting isometrically. In the patient whose muscle was tenotomized, type I fibers decreased in size ($P < .001$) while type II fibers showed only a modest increase ($P < .01$). Individual prestimulation and poststimulation histograms are displayed in Fig 2.

Patient 1 was the first to undergo femoral nerve stimulation, and features of the poststimulation biopsy specimen suggested that the stimulation of certain fascicles of his muscle was excessive. A large number of notably enlarged fibers, confined to a restricted part of the biopsy specimen, was observed. Thirty-five percent of type I fibers and 29.1% of type II were greater than 70μ and many were above 150μ (Fig 3 and 4), a size rarely seen in any human neuromuscular disorder. Rare evidence of fiber splitting was seen. In addition, 16.5% of type I fibers and 46.8% of type II were smaller than 30μ. Many of these fibers were NADH-TR-dark, occasionally angulated, and lacked specific myofibrillar architectural change, features consistent with denervation. Thus, in addition to excessively enlarged fibers, of both types, there was a noteworthy population of atrophic and presumably denervated fibers. These occurred in a scattered manner suggestive of random axonal damage. Because of this wide spread of fiber size, a log transformation of data was carried out to allow proper statistical analysis (Table 2). The presence of denervated fibers of both types suggests that the surgery, mode of stimulation, or mechanical effects of the electrodes caused neural damage to both types I and II axons. The other patients were believed to have had an adequate stimulation program (Fig 5). Both fiber types increased in size to normal values, and in patients 2, 3, and 4, a depleted population of type I fibers was restored without evidence of neuronal injury.

Table 3 lists the changes observed in the degree of staining for oxidative enzyme activity. Fibers staining darkly with NADH-TR also did so for SDH, but since fiber differentiation and counting were easier with the former reaction, this was utilized for the counts. Patient 1 was not included in this Table since the changes in his poststimulation biopsy specimen (hypertrophy, atrophy, clumping, and

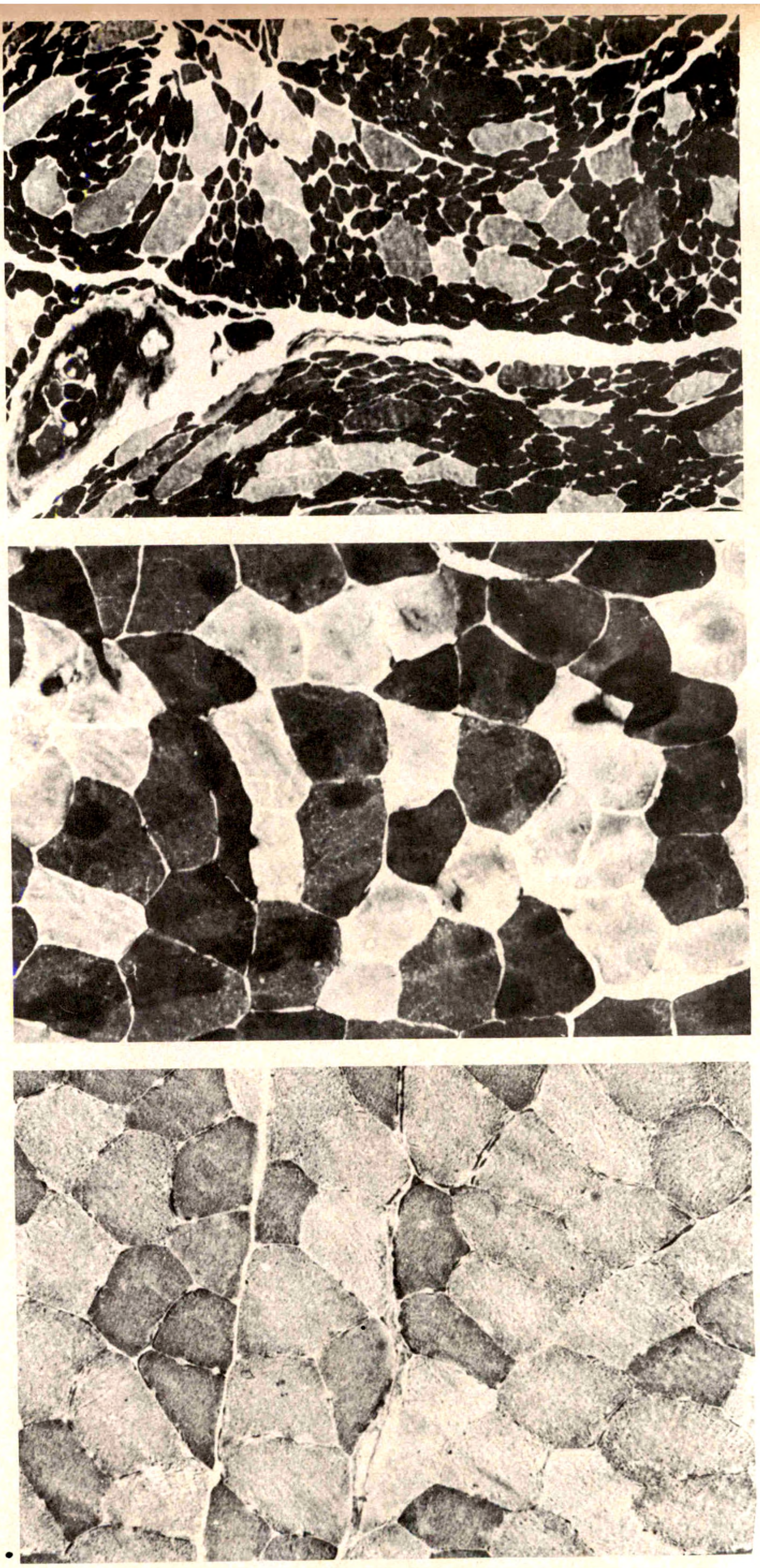


Fig 5.—Biopsy specimens of patient 4. Top, Prestimulation specimen shows type II atrophy (mean diameter, 20.8μ ± 8.8μ). Fascicles and fibers distorted by compression artifact. Center, After ten weeks' stimulation, essentially normal pattern observed for ATPase reaction. Bottom, Essentially normal pattern also observed for NADH-TR reaction. Type II fibers increased in size to 86.2μ ± 18.1μ (original magnification ×150).

whorls) made fiber characterization by the NADH-TR or SDH reactions very difficult. In all patients except patient 5, whose muscle was tenotomized, increases in fibers with high oxidative activity occurred. This would correspond well with the observed decrease in ATPase-dark fibers. In patient 5, the reverse occurred, with a decrease in oxidative-rich fibers (Fig 6 through 8).

One spindle was observed in each of three poststimulation biopsy specimens, and these were all normal as to size and number of intrafusal fibers as well as histochemical profile. No changes were observed in blood vessels or connective tissue.

Changes of uncertain significance in poststimulation tissue were occasionally observed in the pattern of diformazan reaction product in both NADH-TR and SDH reactions. These were most prominent in patient 1 who was possibly overstimulated. Many fibers of both fiber types demonstrated a maldistribution of reaction product (Fig 4). Small fibers (10μ to 15μ) showed clumping and irregular aggregations interspersed with areas devoid of oxidative enzyme activity. Some of the larger and presumably overstimulated fibers, again of both fiber types, showed a peculiar whorled configuration, at times simulating the changes seen in polymyositis and myotonic dystrophy.

Phosphorylase and PAS reactions were essentially normal. In general, there was greater reactivity in type II fibers, regardless of size. No evidence of fibers completely devoid of glycogen was found. It should be noted that the biopsies were carried out several hours after the last epoch of stimulation. Oil red O stains for lipid showed a normal pattern of droplet

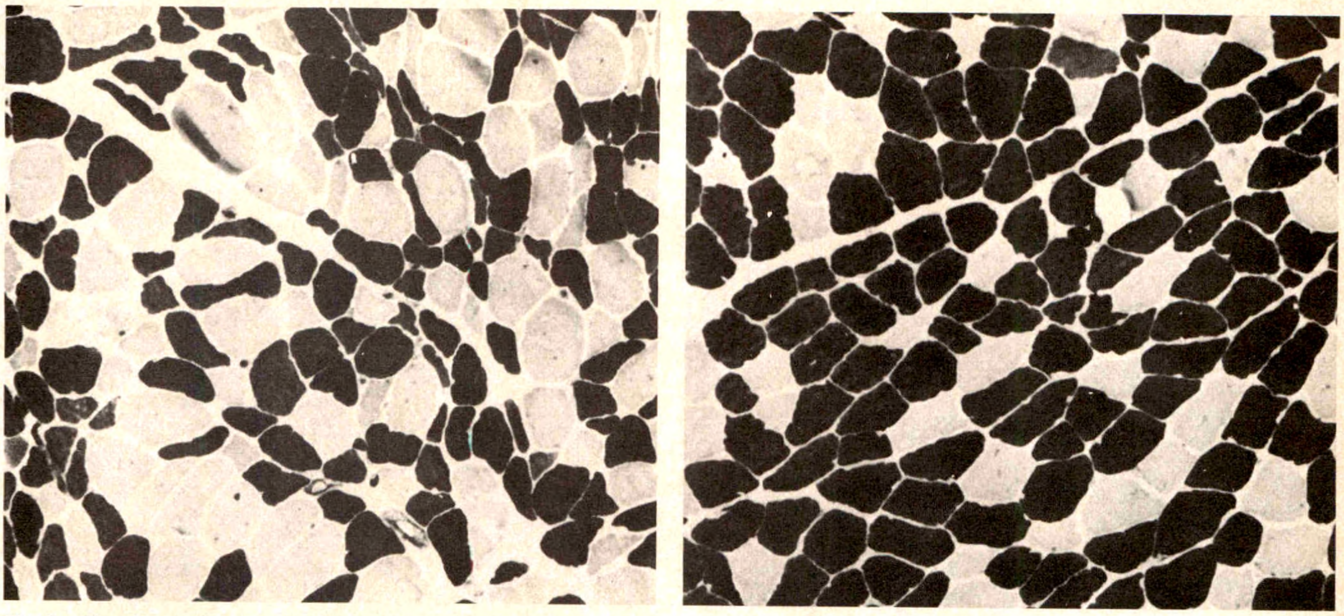
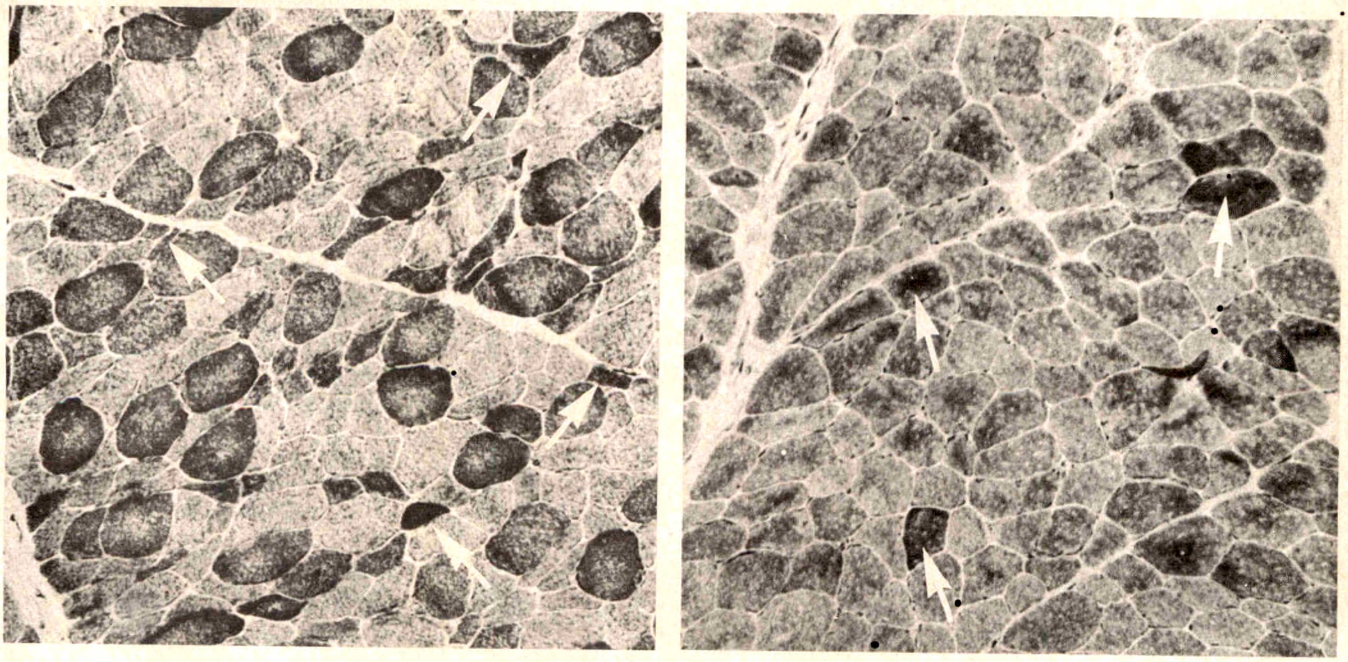


Fig 6.—Biopsy specimens of patient 5. Left, Initial specimen shows type II atrophy. Right, After tenotomy and phasic stimulation, percentage of type II fibers increased, and both types now roughly equal in size (ATPase, pH 9.4, original magnification ×150).

Fig 7.—Biopsy specimens of patient 5. Left, Initial specimen shows small, angulated, dark fibers (arrows) consistent with denervation. Note good differentiation of two fiber types. Right, After tenotomy and 12 weeks' phasic stimulation, loss of all but few large, dark-staining fibers (arrows). Rare denervated fibers still seen. Staining now uniform, and size differential lost (NADH-TR, original magnification ×150).



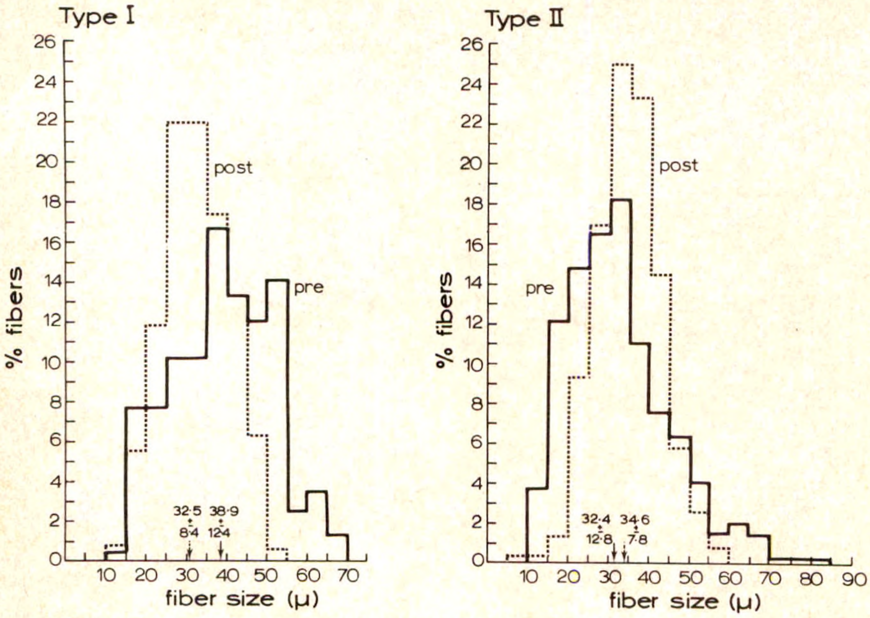


Fig 8.—Initial and poststimulation histograms (patient 5). Mean diameter ± SD, as indicated. Reduction of type II diameter ($P < .001$). Also, type I fibers decreased from 40.2% to 25.4% ($P < .001$).

size, location, and fiber distribution. No evidence of fiber type grouping was seen. Changes of both size and fiber type proportion were more prominent in some fascicles than others. No central cores, necrosis, or nemaline bodies were observed.

COMMENT

These observations confirm for man, as has been demonstrated in animals,[21-26] that muscle fiber characteristics are mutable with artificial peripheral nerve stimulation. In each of four patients, a phasic stimulation program, producing isometric contraction, resulted in an increase in the size of both fiber types ($P < .001$), and in two of these, a conversion of many type II to type I fibers ($P < .001$). In the other two, type I fibers increased less ($P < .05$). In a fifth patient, a similar program of stimulation was carried out on tenotomized rectus femoris. In this patient, type I fiber size decreased ($P < .001$), type II increased ($P < .01$), and the proportion of type I fibers decreased 14.8% ($P < .001$).

Interpretation of Fiber Changes

A certain degree of caution is necessary in interpreting these results. First, is the biopsy technique valid? It seems unlikely that the observed changes in the second biopsy specimen were a result of the surgical trauma occurring during the first. In a previous study,[27] a second biopsy was performed 8 to 21 days after cold injury to muscle, and the demarcation line between normal and regenerating muscle was abrupt and easily recognized. In the present study, the second biopsy was performed at a minimum of five weeks after the first and at a widely separated site. Although considerable variation in fiber type composition occurs in superficial fascicles of different parts of the same muscle (personal observations), these variations appear to be random and would not account for a change in the same direction in each of the four patients in whom muscle contraction was isometric, as was observed. Thus, it seems unlikely that the changes observed were a result of the biopsy technique.

Another consideration is the possibility that the observed shift in fiber type composition with stimulation does not represent a conversion of type II to type I, but rather a selective atrophy and dropout of type II, resulting in an apparent, but not true, increase in type I fibers. Type II fibers are sensitive to a variety of factors leading to preferential type atrophy. These include disuse, steroid effect, and collagen-vascular disorders. "Type II" axons may be more susceptible to the damaging effects of stimulation or the electrode itself. Our observations suggest, however, that this is not a satisfactory explanation. When atrophic, presumably denervated, fibers were observed, they were equally of both types. In addition, in patients 2, 3, and 4, where no evidence of denervation was seen, a noteworthy shift still occurred. We conclude, therefore, that the change in fiber composition observed was an effect of the stimulation program.

Axonal Stimulation

An important aspect of understanding these changes relates to which axons within the nerve trunk are being stimulated. This is not an easy matter. Although fast-twitch units are driven by fast-conducting, large-diameter, and low-threshold axons,[19] these may not be stimulated preferentially with a wraparound electrode. In fact, the equal increase in the size of both fiber types, even though our voltage was approximately 50% maximal, suggests that both axonal "types" were being discharged to a similar degree. Nerve fascicles, as they course along a large peripheral nerve twist, divide and recombine in an unpredictable and random manner.[28] Also, local current density flow will be affected by the trauma and hemorrhage of surgery, the subsequent build-up of epineurial and perineurial connective tissue, and changes in electrode composition. In several areas of the poststimulation material, there appeared to be preferential enlargement of all fibers in a few, usually adjacent, muscle fascicles. This suggests that certain portions of the nerve were being preferentially stimulated. But here again, within these areas, both fiber types were equally enlarged.

Meaning of Observed Changes

One of the more interesting and unexpected observations was the proportional increase in type I fibers in all four patients where contraction was isometric. Stimulation variables were chosen primarily to insure a proper therapeutic result, with safety to the nerve and comfort to the patient. The stimulation program was phasic in nature, ie, short bursts of relatively high-frequency discharge. Although direct measurements have not been carried out in humans, results of studies in animals[19] suggest that motor units discharging in this fashion are fast-twitch and contain high levels of myosin ATPase (type II). Also, it has been demonstrated several times that slow (tonic) programs of peripheral nerve stimulation will convert fast-twitch, type II fibers to slow-twitch, type I.[21-26] We thus expected to find a greater increase in the size of type II fibers and an increase in their relative numbers due to conversion of some of the type I population. In fact, the reverse occurred.

Further information about the possible meaning of this somewhat unexpected result was provided by patient 5, who received an identical program of stimulation to muscle that was tenotomized and thus contracted isometrically at a shortened length and against considerably less resistance. The change in fiber composition in this instance was in the reverse direction. Also, type I fibers showed a decrease in mean size. These observations suggest that the pattern of electrical stimulation was less important than the conditions of the contraction process itself.

Excessive Activity of Muscle

The study of nerve-muscle interaction has been of increasing interest in recent years. Several approaches have been used, primarily in animals, and the results have bearing on the interpretation of our observations. Exercise alone can induce metabolic alterations in skeletal muscle. Increased oxidative enzyme activity occurs in both guinea pig[29,30] and rat.[31] In man, a general training program for fitness can convert type II to type I fibers, but only in younger males, not the middle-aged.[32] The ATPase activity[30,31] and contractile properties[33] are more resistant to change than oxidative capacity.

Excessive use of a muscle can also be induced experimentally by inactivating synergistic muscles. Such studies have shown prolongation of contraction time accompanied by a decrease in ATPase activity.[34,35] Conversely, inactivating antagonistic muscles[36] leads to the reverse type of change; the muscle becomes physiologically faster, and ATPase activity increases.

In studies utilizing artificial peripheral nerve stimulation in animals,[21-26] all but one[26] utilized a slow rate of stimulation (10 Hz) to fast muscle. The results of these studies are in reasonable agreement. Physiologic slowing was accompanied by appropriate biochemical and histochemical changes. Peckham et al[37] achieved similar results with 10-Hz motor point stimulation in cats and one human.[38] In both of these studies, a shift toward slow muscle occurred. Salmons and Vrbova[21] and Al-Amood et al[25] studied only physiologic variables, while the histochemical studies of Peckham et al[37] were limited to SDH. Pette et al,[24] stimulating fast muscle at 10 Hz for up to 28 days, noted only type I and intermediate fibers remaining, but fiber typing was based on SDH activity alone. Regressive changes were observed after four weeks of stimulation. Riley and Allin[26] studied ATPase after both low and high rates of stimulation, and although the expected oxidative enzyme changes occurred, ATPase remained refractory.

To summarize these experiments, muscle stimulation of any form seems to result in physiologic slowing accompanied by an increased number of fibers with low ATPase and high oxidative activity. Speeding of slow muscle appears more difficult to accomplish, although sufficient experiments have not yet been carried out.

Inactivation of Muscle

Conversely, inactivated muscle tends to become physiologically faster,[39-41] with fibers containing more ATPase activity and less oxidative capacity.[42-44] The mode of inactivation does not appear to be critical. Thus, similar changes have been reported with tenotomy,[45] joint fixation,[39] cordotomy with posterior root section,[41] and cordotomy alone.[40]

In 1959, Sunderland and Lavarach[46] examined paraffin-embedded muscle obtained at autopsy from two patients who had undergone amputation 20 years and ten months previously. All the "tenotomized" muscles examined were reduced in size and weight, and those subjected to the greater disuse showed the greater reduction, which varied from 39% to 60%. Patchy "degenerative" changes were noted only in rare scattered fibers. Their published photomicrographs, however, show a suggestive pattern of fiber type atrophy of one of the major fiber types. This constitutes the only human study on tenotomized muscle we have been able to find. In our patient, other than fiber size and histochemical composition, there was no specific change. In rat soleus, Awad and co-workers[47] have reported myofibrillar loss and vacuolar changes, with loss of lactate dehydrogenase, aldolase, and ATPase activity. Hikeda[48] has recently reported a shift of ultrastructural characteristics toward a fast type of muscle. Other changes in tenotomized animal muscle have included necrosis, phagocytosis and granular degeneration,[42] target cells and sarcoplasmic masses,[42] nemaline bodies,[42,49,50] and central cores.[42,50] None of these were observed in our patient after 12 weeks of tenotomy. It is possible that the stimulation program prevented these features.[51]

Nerve Dependence

The question of whether these changes are nerve dependent or not, has been the subject of considerable discussion. The hallmark cross-reinnervation studies of Buller et al,[52] in which a fast or slow muscle is reinnervated by a nerve supplying a muscle of the opposite type and assumes the physiologic, biochemical, and histochemical characteristics[53,54] of the previously innervated muscle, suggested to many that the metabolic profile of muscle was nerve-determined; either through a process of programming by transmitter release or by other as yet unidentified neuronal "trophic substances." In some of his early studies, Eccles[55] was not able to prevent atrophy of tenotomized, slow muscle with percutaneous electrical stimulation. He concluded that neither the pattern of stimulation nor the total number of stimuli could prevent these regressive changes. Others, however, felt that the pattern of neuronal discharge was important in preventing the degenerative changes observed with tenotomy. Thus, slow rates of stimulation, but not high, prevented various degenerative alterations in slow muscle.[51]

More recently, more precise experiments that have attempted to dissociate nerve and muscle function suggest that nerve influences may be somewhat less important than initially thought. Thus, muscle deprived of its neuroelectrical control by anesthetic block[56] or even fully denervated[57,58] is able to maintain its bulk as well as physiologic and biochemical characteristics if caused to contract by other means. Even rhythmical passive stretching[59-61] of denervated muscle will prevent certain effects of denervation for short periods of time.

In recent discussions of the effects of nerve on muscle, little attention has been given to the importance of resting length and resistance during contraction as determinants of myofiber profile. In 1944, Eccles[55] observed that atrophy of tenotomized muscle was greater if it contracted at a shortened length without resistance. Ralston and associates[62] noted greater weight and protein loss in muscle immobilized at a shortened length. These deleterious effects of inactivity are more prominent in slow muscle than in fast.[55] In discord with these observations is the fact that in humans disuse is associated with preferential atrophy of fast-twitch (type II) fibers.[63-64]

CONCLUSIONS

These observations suggest (1) that the neural component of the motor unit may be acting in a rather passive manner as a conduit for central nervous system information, (2) that the pattern of neuronal discharge is somewhat less important than the conditions of contraction per se, and (3) that self-regulatory mechanisms within the myofiber itself are important. The results reported in this article are in agreement with this point of view. Although a phasic pattern of stimulation was utilized, the type of conversion that occurred was determined not by the pattern of stimulation, but rather by the physical conditions of contraction. If muscle contracted isometrically, at a lengthened position and against resistance, stimulation resulted in an increased proportion of type I fibers, with an increased size of both types I and II. If, on the other hand, the muscle contracted isotonically, at a shortened length and with lesser resistance, type I fibers decreased proportionately in numbers and size.

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Cervical Spondylotic Radiculopathy and Myelopathy

A Long-Term Follow-up Study

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• **The natural history of cervical spondylotic myelopathy in a series of 55 patients resulted in a moderate to severe disability during a mean period of 45 months. Results of operation for myelopathy indicated improvement in one group that was maintained for a mean of 85 months. In another group, progressive worsening occurred after operation, or late worsening occurred, in some instances as long as 8 to 12 years after improvement and plateau. Patients with cervical spondylotic radiculopathy tended to be separated from those with myelopathy with respect to presentation, symptom complex, and operative result. Results of operation for radiculopathy were consistently good.**

A worsened disability postoperatively for patients with cervical spondylotic myelopathy was associated with the preoperative symptom of sphincter disturbance and the sign of lower extremity weakness. Change in hand movement after operation for myelopathy and change in distance walking ability were not correlated with numerous preoperative factors. A trend of improvement in disability following anterior interbody fusion and a tendency to worsen in disability following all varieties of laminectomy were significant.

(*Arch Neurol* 33:618-625, 1976)

Surgical treatment for cervical spondylotic myelopathy has yielded a wide range of results. Analysis of these data has indicated that several preoperative factors may play a part in the outcome. Advanced age prior to admission as well as a short duration of preoperative symptoms have been associated with a poor result.[1,2] Although preoperative neurological findings such as intrinsic hand muscle atrophy have been implicated in worsening, other findings, such as severe lower extremity spasticity, have not.[3,4] Furthermore, advocates of different surgical procedures have claimed variable results following operation for cervical spondylotic myelopathy.[5,6] Despite implications that each of these symptoms, signs, and surgical procedures may affect worsening or improvement, there has been no comprehensive statistical analysis of results in a surgical series with long-term follow-up.

Operations for cervical spondylotic radiculopathy have produced better results than have procedures for myelopathy, although some failures have been noted. In one report,[7] single-level anterior interbody fusion in the presence of multiple-level disease has been linked to worsening postoperatively. However, retrospective studies considering patients with radicular disease separately from those with myelopathy have been too few to draw conclusions concerning results.

We have recently retrospectively reviewed a series of 96 patients who underwent operation for severe cervical spondylotic myelopathy and radiculopathy, with a mean follow-up of more than seven years. Our purpose in this study was to determine, with use of computerized data and statistical procedures, those factors in the history, examination, and surgical management that might influence long-term success or failure.

SUBJECTS AND METHODS

Ninety-six patients, 63 men and 33 women, comprised this retrospective study group. Their average age at onset of symptoms was 51 years, and at time of admis-

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sion, it was 53 years. They were classified into myelopathy (55 patients) and radiculopathy (41 patients) groups, on the basis of presenting signs and symptoms. All had undergone one operation, either at the UCLA Hospital or the Wadsworth Veterans Administration Hospital, Los Angeles, and all had had neurological examinations prior to operation. All patients had a progressively worsening condition despite conservative methods of treatment.

The surgical procedure utilized was anterior interbody fusion done by the Cloward technique in 62 cases, and laminectomy in 30 cases. Four patients underwent posterior lateral laminectomies with foramenotomies.

Each of the 96 cases was analyzed separately in terms of factors that might have been involved in outcome (Box). Four outcome variables were designated. The first outcome variable consisted of the five-category postoperative disability evaluation of Lees and Turner[8] with the modification of Symon and Lavender,[9] combined into three categories. The absence of disability and the mild disability categories were placed in one class, the severe bedridden and severe nonbedridden disability categories into another class, and the moderate disability category was designated as the third class. In addition, the four-category overall evaluation scheme of Crandall and Batzdorf[10] was combined into two groups and used as the second outcome variable. The "excellent" and "improved" categories were included as one group, and the "unchanged" and "worsened" categories as another. The final two outcome variables were changes in fine hand movement and distance walking; these were noted as improved, unchanged, or worse.

Data were coded and analyzed, using BMED programs and the HSCF 360-91 computer.[11] Scanning, editing, and frequency distribution were done by the BMD P2D computer program. Analysis was accomplished with use of the BMD P1F two-way contingency table program. Data processing was carried out on the IBM 360-91 computer.

Chi-square tests were used to evaluate the independence of the row and column classifications. The regression coefficient in conjunction with partitioning of the χ^2 was employed to analyze the data for linearity. The Fisher exact probability statistic was used to refine further the χ^2 in 2×2 tables with small numbers. Results were considered highly significant at $P \leq .005$, significant at $P \leq .05$, and approaching significance at $P > .05$ if $\leq .06$.[12]

Factors Used in Comparison to Outcome Variables

1. Age
2. Sex
3. Race
4. Presence or absence of forced neck movement prior to operation
5. Presence or absence of injury related to onset
6. Chief complaint on admission
7. Preoperative symptoms:
    - Lower cervical pain
    - Lhermitte phenomenon
    - Sphincter disturbance
    - Lower extremity weakness
    - Radicular pain
    - Extremity numbness
    - Upper extremity weakness
    - Gait
8. Clinical root involved
9. Age at symptom onset
10. Age at admission
11. Signs present on admission physical examination:
    - Spasticity, upper extremity
    - Spasticity, lower extremity
    - Weakness, proximal part of upper extremity
    - Spasticity, lower extremity
    - Atrophy, proximal part of upper extremity
    - Atrophy, distal part of upper extremity
    - Spinothalamic deficit
    - Dorsal column deficit
    - Dermatological sensory deficit
    - Loss of neck range motion
12. Category of myelopathy (Crandall and Batzdorf, 1966[10])
13. Preoperative disability class
14. Impairment of fine hand movement prior to operation
15. Impairment of distance walking prior to operation
16. Plain x-ray film: (1) level of anterior bar;
    (2) level of foraminal obstruction
17. Oil myelogram: presence or absence of block
18. Air myelogram: presence or absence of block
19. Cerebrospinal fluid protein
20. Surgical procedure:
    - Anterior interbody fusion
    - Laminectomy: dura open, dura closed, dentate ligaments cut, dural graft
    - Posterior lateral foraminotomy
    - Number of levels and location of each level
    - Complications
    - Presence or absence of atrophy at operation
21. Postoperative factors: (1) day mobilized;
    (2) weeks in collar or brace
22. Months of follow-up after operation

Follow-up Data

All patients underwent periodic postoperative examination in the clinic. Additional follow-up data were obtained by telephone contact, chart review, questionnaire, or examination by one of us or another member of the neurological or neurosurgical faculty or residency staff. Final follow-up information was obtained as follows: (1) by extensive telephone interview with 72 patients, many of whom had undergone recent neurological examination in the clinic; (2) by physical examination in six patients; (3) by questionnaire in three; and (4) by chart review in 15. Our data were thus somewhat biased. Final follow-up time averaged 85 months (range, 24 to 247 months). Forty percent were followed up from 24 to 60 months; 28%, from 61 to 120 months; and 32%, from 121 to 247 months.

RESULTS

Radiculopathy

Signs and Symptoms.—Radicular pain was present in more than one half of the radiculopathy cases. Although the mean onset of symptoms was 32 months to hospital admission (range, 1 to 144 months), 46% of patients were admitted one year or less from onset, and 63% of patients were hospitalized two years or less from onset. The pattern of onset of the pain was slow and progressive in most cases. When all symptoms and signs at admission were considered, a large variety was seen (Fig 1 and 2).

In addition to their primary radiculopathy, six patients had slight evidence of mild spasticity, weakness, or a clinically detected gait disturbance (none of which had been evident to the patient) attributed to cord compression. Four of these six patients had no preoperative disability due to their myelopathy. Five other patients had atrophy in the intrinsic muscles of the hands with plain roentgenographic evidence of osteophytes at higher levels. Two others complained of radicular pain and had radiographic evidence of osteophytic spurs and pain on neck range of motion, with no positive neurological findings on examination.

By the time of admission, disability was severe in most patients (Table 1). Only three were able to carry out their work unhindered. Twenty were moderately disabled and 15 were classified in the severe nonbedridden group. The three uncounted patients were those in whom preoperative but not postoperative disability information was available.

Indications for Operation.—The common indication for operation was the presence of chronic, unremitting radicular pain or chronic cervical pain, accompanied by numbness in a radicular pattern, aggravated by Spurling maneuver. This was usually associated with cervical foraminal osteophytes demonstrated in plain roentgenograms and pantopaque myelograms. Atrophy or muscular weakness per se was not used as primary indication.

Surgical Technique.—Thirty-six patients had the Cloward technique of anterior interbody fusion.[13] Sixteen patients were fused at one level, 19 at two levels, and one at three levels. The three-level fusion was in a patient with predominantly radicular pain, although mild myelopathy was present, together with multiple-level disease. Posterior lateral laminotomy and foramenotomy was used four times, one of these at two levels. One laminectomy was done in a patient with prominent radiculopathy, mild myelopathy, and multiple osteophytes.

Postoperative Results.—Results of operation were tabulated after a mean follow-up period of 7.3 years. Based on the overall evaluation scheme previously explained, for which all patients were evaluated, 13 were classified as excellent, 18 improved, five unchanged, and five worse. According to the disability grading system, for which only 38 patients could be evaluated, 24 had no disability, ten were in the moderate category, and four were in the severe nonbedridden category (Table 1). Of those 25 patients improving, 11 im-

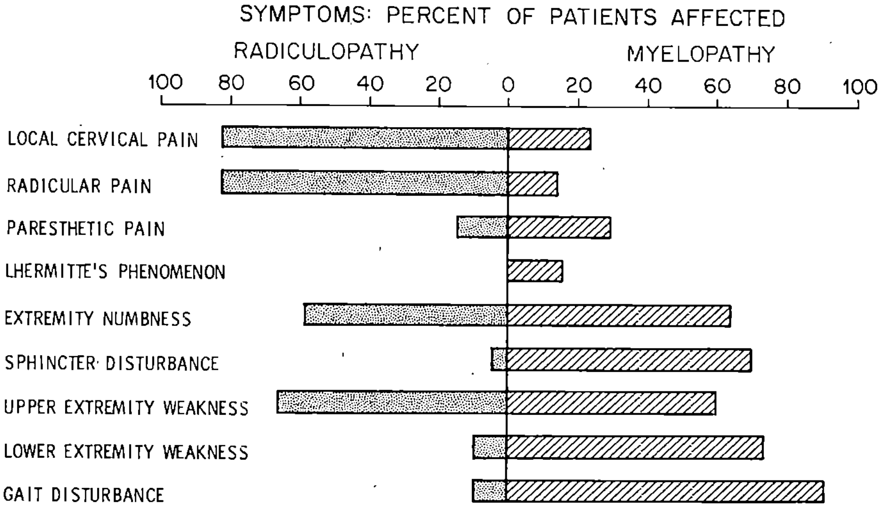


Fig 1.—Symptoms at admission in radiculopathy and myelopathy groups. Included are all symptoms in all patients.

Fig 2.—Physical findings at admission in radiculopathy and myelopathy groups. Included are all signs found in all patients. UE indicates upper extremity; prox, proximal part; LE, lower extremity; derm, dermatomal; ROM, range of motion.

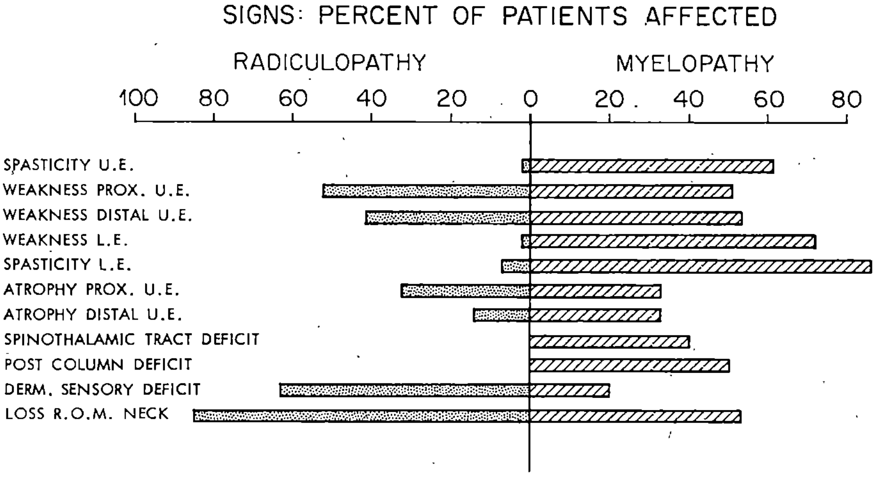


Table 1.—Comparison of Preoperative and Postoperative Disability in Patients With Radiculopathy

	Preoperative Disability			
Postoperative Disability	**Mild**	**Moderate**	**SNB-SBR***	**Total**
Absent-mild	(2)†	13	9	**24**
Moderate	1	(6)	3	**10**
SNB-SBR	0	1	(3)	**4**
Total	**3**	**20**	**15**	**38‡**

*Severe nonbedridden-severe bedridden.

†Numbers in parentheses denote patients whose conditions remained unchanged after operation.

‡Three patients not counted.

proved in two categories, and one improved in three categories. The latter was a 45-year-old woman with a C6,7 radiculopathy who underwent a two-level anterior interbody fusion and has remained symptom free for 12 years. In addition, 13 patients either did not change or worsened in disability.

Twenty-four patients with radiculopathy had preoperative impairment of fine hand movements due to weakness, numbness, or atrophy. Sixteen of these were improved and four others were worse postoperatively.

Time intervals to maximum improvement, plateau, or worsening of fine hand movements have been obtained in 15 patients postoperatively. Six regained fine hand movements within one month after operation, and eight reported maximum improvement in the first year after operation. One reported full return at three years. The improvement has been maintained for intervals up to 14 years in all patients but three. Two of these three lost function ten years and 12 years postoperatively. The time could not be accurately determined in a third.

Other patients with radiculopathy have maintained their improvement or unchanged status during the follow-up period, a mean of 88 months (range, 24 to 190 months). The six patients with definite mild myelopathy in this group were followed up for a mean of 60 months. Two are in the overall improved category, and one has had regression of radiculopathy symptoms with no regression of his myelopathy. Two others had no abatement of their pain with no progression of myelopathy. The final patient has clearly progressed in lower extremity weakness and spasticity. The 35 who did not have myelopathy initially have remained unaffected.

Data Analysis.—There was no significant relationship between outcome variable and any preoperative symptom, such as radicular pain, neck pain, or numbness, or any sign such as extremity numbness. In addition, the signs of mild spasticity, lower extremity weakness, and gait disturbance, indicative of myelopathy in the radiculopathy group, were not associated with outcome.

Outcome of operation was generally good in the radiculopathy group. Of 41 patients, 31 were in the excellent and improved category and ten were in the unchanged or worse category. Further, 24 patients were in the absent or mild postoperative disability class (Table 1).

The surgical procedure for radiculopathy was either anterior interbody fusion (36 cases), posterior lateral laminectomy (four cases), or laminectomy (one case). The latter two types were combined for comparison. Comparison of operative procedure to postoperative disability and overall evaluation indicated that the patients with either procedure had a good result, despite a poor *preoperative* disability in the anterior interbody fusion group.

Myelopathy

Signs and Symptoms.—When all symptoms on admission were considered, gait disturbance and lower extremity weakness were most common (Fig 1). Radicular pain in eight patients reflected the degree of nerve root compression. This was disabling in only one patient; in the others, it was intermittent and not severe.

The symptoms of myelopathy began insidiously and were slowly progressive in the majority of patients. Because this disease was slowly progressive, 22% of patients tolerated their symptoms from 5 years to 25 years before admission to the hospital. Many had trials of conservative therapy, such as a collar or physical therapy, before admission. The mean onset of symptoms was 45 months prior to admission (range, 1 to 313 months).

Results of physical examination on admission revealed a variety of signs (Fig 2). Most prevalent were spasticity and weakness in the lower extremities. However, spasticity and weakness in the proximal and distal parts of the upper extremities were also frequently observed.

Patients were divided into categories according to the predominant cord syndrome.[10] Twenty-eight patients were categorized into the transverse myelopathy group, with evidence of corticospinal tracts combined with either posterior column or spinothalamic tract involvement. A predominant motor system syndrome was noted in 20 patients, who had evidence of severe corticospinal tract, with or without anterior horn cell involvement and with an often present but relatively insignificant sensory deficit. Less commonly, some patients (five) were found to have a Brown-Sequard syndrome, with an ipsilateral corticospinal deficit and contralateral analgesia below the level of the lesion; one other patient had a central cord syndrome with upper extremity weakness and sensory loss sparing the lower extremities. Although eight patients had radicular pain, the accompanying cord syndrome appeared to be variable, and these patients could not be categorized in a group.

By the time of admission, disability had usually become quite severe. Initially, only one patient was in the mildly affected category (Table 2). In contrast, 26 were moderately affected and 24 were in the severe nonbedridden category. Two others had reached the severe bedridden category by admission. Fine hand movements had become affected to a variable degree in 39 cases, while distance walking ability had become mildly to severely impaired in 49 patients.

Indications for Operation.—The most common indication was progressive decline in spinal cord function. With circumstances of chronic cervical intervertebral degeneration at multiple levels (three or more), narrow sagittal diameter of the spinal canal (< 13 mm), lordosis, and telescoping of the laminae, or "shingling," the operation of cervical laminectomy was generally carried out.[10] When radiographic studies indicated chronic cervical degenerative disease with impingement on the spinal cord at one to two interspaces, the operation of anterior cervical disk excision and interbody fusion was generally performed. In addition, if the radiographic studies demonstrated fixed cervical kyphosis, despite the multiple-level involvement, the anterior operation was selected to relieve the anterior cord pressure.

Surgical Technique.—Twenty-six patients underwent anterior interbody fusion by the Cloward technique. Nine single-level, 16 double-level, and one triple-level fusions were performed.

Twenty-nine patients underwent laminectomy. The type of laminectomy done by different surgeons was varied in certain details. However, the common purpose was to enlarge the cervical spinal canal by a long laminectomy. Twenty patients had five or more levels resected (C3 through C7). Five patients had four, and four patients had three levels removed. A dural graft to enlarge the canal was placed 12 times and one such patient also had the dentate ligaments cut. The dura mater was left open in one patient. The dentate ligaments were sectioned in eight patients, after which the dura mater was closed.

Postoperative Results.—Long-term

Table 2.—Comparison of Preoperative and Postoperative Disability in Patients With Myelopathy

Postoperative Disability	**Preoperative Disability** **Mild**	 **Moderate**	 **SNB-SBR***	**Total**
Absent-mild	(1)†	3	5	**9**
Moderate	0	(11)	9	**20**
SNB-SBR	0	12	(12)	**24**
Total	**1**	**26**	**26**	**53‡**

*Severe nonbedridden-severe bedridden.

†Numbers in parentheses denote patients whose conditions remained unchanged after operation.

‡Two patients not counted.

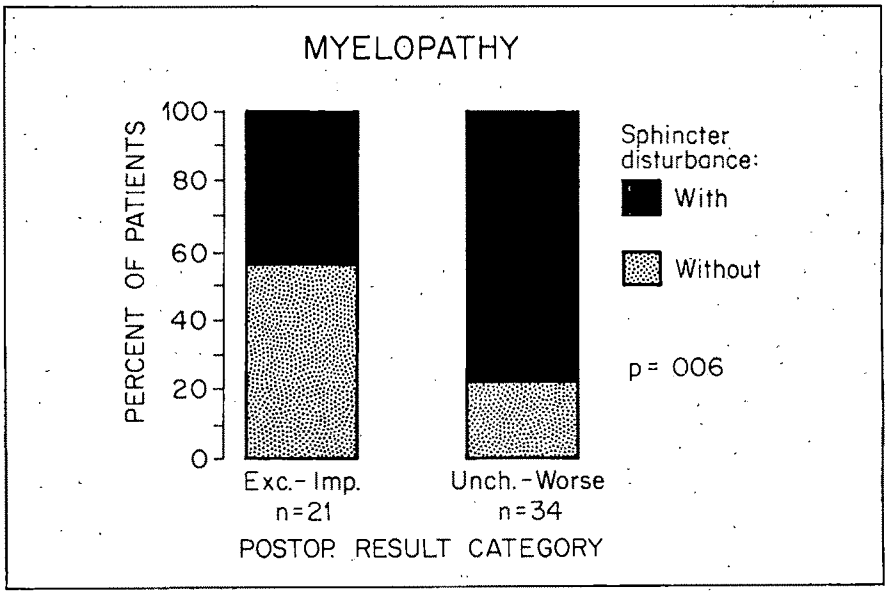


Fig 3.—Percentage of patients with preoperative symptom of sphincter disturbance in each postoperative result category. Excellent and improved categories as well as unchanged and worse categories are combined. N is equal to number of patients in each result category. Exc-imp indicates excellent to improved; unch, unchanged.

Fig 4.—Comparison of preoperative and postoperative disability in 15 myelopathy patients undergoing anterior interbody fusion who changed in at least one disability class. SNB indicates severe nonbedridden; SBR, severe bedridden; mod, moderate.

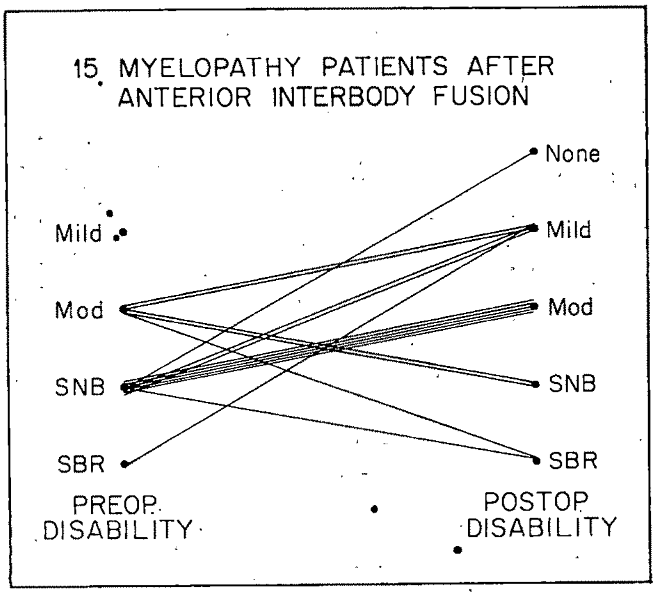
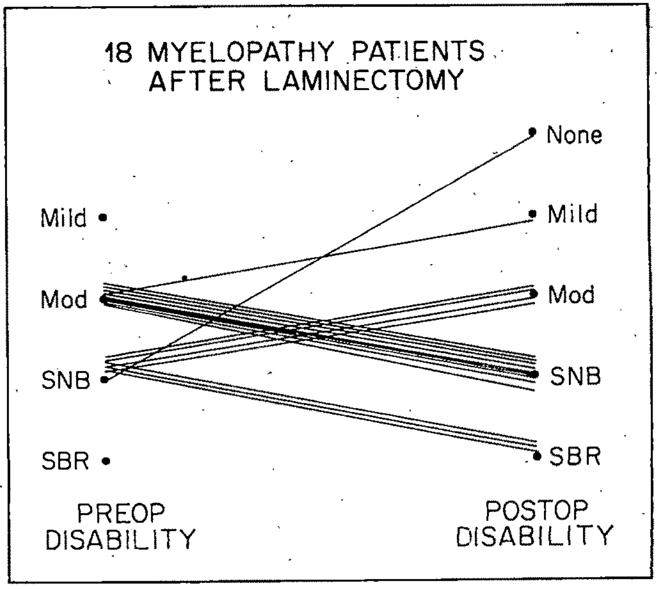


Fig 5.—Comparison of preoperative and postoperative disability in 18 myelopathy patients undergoing laminectomy who changed in at least one disability class. Mod indicates moderate; SNB, severe nonbedridden; SBR, severe bedridden.



results of operation were not as good in the radiculopathy category: 21 were excellent or improved, ten were unchanged, and 24 were worse. From the standpoint of postoperative disability in 53 of the myelopathy patients, nine were unimpaired at full-time work, 20 were in the moderate category, and 24 were severely disabled (Table 2). Twenty-four patients remained unchanged from their preoperative disability, 17 improved, and 12 worsened. In addition, four other patients declined from the severe nonbedridden to the severe bedridden category. Twelve patients improved in two categories. There were some dramatic recoveries. Two patients changed from the severe nonbedridden category to no disability postoperatively. One, a 46-year-old construction worker with a transverse myelopathy syndrome who underwent a C4,5,6 laminectomy with section of the dentate ligaments and placement of a dural graft, has returned to construction work and has exhibited no disability for 174 months of follow-up.

Forty-three patients changed with respect to ability to walk distances. Nineteen improved and 24 worsened. Fifteen patients noted when their distance walking improved. Maximum improvement occurred in 11 of these by six months, and in the other four, by two years. All have maintained their maximum improvement 21 months to 20 years since operation.

Another group of 11 patients initially improved in distance walking, then stabilized for a time, then worsened due to progressive weakness or stiffness. In all but one, maximum improvement occurred two years or less after operation. Plateau periods from 1 month to 18 years preceded deterioration.

Of the eight myelopathy patients with radicular pain prior to operation, six had no recurrence of pain after operation. With regard to their myelopathy, three of these improved, two worsened, and one remained unchanged. Two patients had an exacerbation in radicular pain after operation, and both experienced worsened disability because of the recurrent pain.

Data Analysis.—Sphincter disturbance was the only preoperative symptom related to outcome. Although prior to operation this symptom often was manifested only by mild loss of urinary control or urgency unassociated with need for a catheter, there was a highly significant linear association between its presence and postoperative disability ($P = .001$). A significant association was also discovered between the presence of sphincter disturbance and overall evaluation after operation ($P = .006$ [Fig 3]). Other symptoms such as radicular pain, lower cervical pain, numbness in an extremity, and weakness in an extremity were not significantly related to outcome.

Lower extremity weakness showed a significant linear association with worsened disability after operation ($P = .01$). No association was found between outcome variables and lower extremity spasticity. Other admission physical findings, such as atrophy in the proximal or distal parts of the upper extremities, decreased range of motion of the neck, and posterior column or segmental sensory deficits, were also not significantly related to outcome variables. In addition, a dermatomal sensory deficit, which marked those patients with radiculopathy in the myelopathy group, was unrelated to outcome.

Fine Hand Movement and Walking Distance Change.—Fine manipulations of the hands, such as the ability to find change in the pockets and to button shirts, was lost in 39 patients prior to operation. Such fine hand movements partially or completely recovered in 15 patients after operation, but worsened in 16 others. The change could not be predicted by preoperative factors. The signs of atrophy of the intrinsic muscles of the hands, upper extremity spasticity, and distal upper extremity weakness were not significantly related to postoperative hand movement change.

Preoperative ability to walk was diminished in 49 patients. Nineteen improved and 24 worsened postoperatively. No relationship could be established between worsening ability to walk distances after operation and preoperative signs. However, patients having symptoms less than 12 months prior to operation had a better prognosis for postoperative walking than did patients with symptoms present longer than 12 months. This approached linear significance.

Surgical Procedure.—Although the method of the posterior laminectomy varied in some details, all techniques of this approach were combined for comparison of results. Because the myelopathy groups in general had progressed to a severe disability prior to operation, each type of surgical procedure was performed on a group equally disabled. Of 15 patients undergoing anterior interbody fusion who changed in disability, five were moderately disabled and ten were in the severe nonbedridden/severe bedridden category (Fig 4). Of 18 patients undergoing laminectomy who changed in disability, ten were moderately disabled and eight were in the severe nonbedridden/severe bedridden category (Fig 5).

The comparison of surgical procedure and postoperative disability showed a linear relationship that approached but did not achieve significance. However, when type of operation was compared with change in disability, ie, those 17 patients who improved in at least one disability class and those 12 patients who worsened in at least one disability class, there was a significant relationship ($P = .035$). In patients who underwent anterior interbody fusion, postoperative disability tended to decrease, whereas in those who had laminectomy, postoperative disability generally increased (Fig 4 and 5). Technical variations of the posterior approach, such as the use of a dural graft or section of the dentate ligaments, had no statistical relationship to improvement or worsening in any category of result. In addition, numbers of levels of anterior interbody fusion had no relation to result.

Other Factors and Relationship to Outcome Variables.—Additional factors were compared with postoperative disability, overall evaluation, change in ability to walk distance, and change in fine hand movements after operation. Neither sex, race, age at symptom onset, age at admission, cerebrospinal fluid protein, months of follow-up, nor numbers of levels of involvement in plain x-ray films were associated with these outcome variables.

Cervical spinal cord atrophy was present on air myelograms or by direct observation at operation in five of seven times. Sixteen patients had a partial or complete myelographic block to pantopaque or air. Five of these had atrophy of the cervical cord distal to the block. Myelograms in 26 other patients showed impingement of the osteophyte in the cord with no block. There was no relationship between these findings and results.

COMMENT

Preoperative symptoms and admission physical findings of patients with cervical radiculopathy and myelopathy (in this somewhat biased retrospective study) were similar to those previously described.[8,10,14] However, the majority of our myelopathy patients had either a transverse cord syndrome or a syndrome with predominant motor system involvement. Radicular pain, present initially in eight myelopathy patients, influenced outcome in only four. Pain did not reappear in the four patients who experienced it initially and did not occur as a new symptom in the 46 patients who did not have it initially. The data from improved patients with myelopathy tend to support the contention that operation may reverse the progression of myelopathy in some patients and it may remain reversed over a long period of time.

Patients with myelopathy most frequently worsened as follow-up lengthened. However, certain patients with myelopathy had a late deterioration following an initial improvement and a subsequent plateau following operation. This may occur as late as six to eight years after operation. In another group of improved patients, no further evidence of deterioration has occurred except for one patient, who has lost function but is still better than he was at the preoperative level.

Cervical spondylotic radiculopathy appears to have a different course from cervical spondylotic myelopathy. The progression from onset of symptoms to admission was shorter (mean symptom onset, 31 months vs 47 for myelopathy), the symptom complex was different (increasing pain vs progressive lower extremity weakness), and five of the six patients with radiculopathy and mild signs of myelopathy had no progression of their myelopathy at last follow-up. This is in agreement with the observations of Lees and Turner.[8]

Evaluation of surgical results and prognosis for radiculopathy by the criteria of change in fine hand movements, preoperative and postoperative disability, and the overall evaluation scheme proved to be consistent during the entire follow-up period. Exceptions were three patients in whom late deterioration in fine hand movements occurred.

Ultimate success or failure of the surgical procedure in the myelopathy group could not be predicted by the preoperative presence or absence of most numerous chief complaints, clinical symptoms, and physical findings. Exceptions were the symptom of sphincter disturbance and the preoperative physical finding of lower extremity weakness. A worsened preoperative disability class was associated with the presence of each, as well as a worsened overall result with the presence of sphincter loss.

Although frequently tabulated as a part of the symptom complex of cervical spondylotic myelopathy, sphincter impairment has not previously been associated with a worsened postoperative result. This connection may be explained on the basis of sphincter disturbance being a symptom of severely advanced spinal cord disease. However, many of the other symptoms and signs in our series were bilateral, advanced, and not statistically associated with a worsened outcome variable. Furthermore, sphincter disturbance as a symptom was often slight and not associated with complete loss of bladder control. The loss of bladder and bowel control, when due to cervical spondylotic myelopathy, is often reversible following operation.[14]

In our series, cervical corticospinal tract involvement was more frequently manifested by signs of lower extremity spasticity than lower extremity weakness. However, the presence of lower extremity weakness rather than spasticity was related to a worsened postoperative disability. This is consistent with a previous observation that severe preoperative spasticity is not necessarily associated with a poor outcome.[4] Perhaps weakness in the lower extremities is an index of more advanced cervical cord compromise than lower extremity spasticity. In addition, the disability classification, of Lees and Turner,[8] which we employed, is based on job performance, which probably would be more affected by lower extremity weakness than lower extremity spasticity.

Change in fine hand movements following operation was not significantly related to the presence of the preoperative signs of weakness of the distal part of the upper extremity, upper extremity spasticity, or intrinsic hand muscle atrophy. Similarly, change in the ability to walk distance could not be predicted on the basis of the preoperative presence of lower extremity spasticity, weakness, or a gait disturbance. However, our study did not take into account severity of spasticity or weakness. This may have influenced the absence of associations among these factors.

Much of the recent literature on cervical spondylotic myelopathy has been devoted to the relative merits of the anterior and posterior approaches in the surgical correction of this disease. Our study reveals an improved postoperative change in disability following anterior interbody fusion. Conversely, a worsening in disability was found after laminectomy. Although widely varying techniques of the posterior approach, such as laminectomy with dentate ligament section and laminectomy with a dural graft, were considered as one group, no significant association was found when each separate type of posterior approach was compared with outcome variables. Furthermore, there were notable excellent results with long-term follow-up after certain cases of laminectomy. Thus, on the basis of our study, we cannot recommend one procedure or the other. However, our data do indicate a trend of improvement on long-term follow-up in disability following anterior interbody fusion and a tendency to worsen in disability after all variables of laminectomy. This is strengthened by the fact that both groups were in similar preoperative disability situations.

The myelographic finding of block to the flow of contrast material was not necessarily associated with a poor result. This may have been due to several factors. In our institution, patients with severe myelopathy and a block to flow of contrast are considered to have an urgent condition and are usually decompressed from either an anterior or a posterior approach soon after the myelographic block is recognized. In addition, the mean duration of symptoms in these patients was greater than three years prior to admission. Because of this, the development of the block was probably slow and not acute, making loss of function recoverable.

Atrophy of the cervical spinal cord seen on air myelogram or at operation did not necessarily imply a poor result. Also, our study did not verify the previous observation that age at admission affected outcome. We did not find that number of radiographic levels of disease was associated with results.

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Anticonvulsant Drug Mechanisms

Phenytoin, Phenobarbital, and Ethosuximide and Calcium Flux in Isolated Presynaptic Endings

Richard S. Sohn, MD, James A. Ferrendelli, MD

• Phenytoin, phenobarbital, ethosuximide, and procaine hydrochloride were evaluated for their ability to inhibit Ca^{2+} flux into isolated presynaptic endings (synaptosomes) prepared from rabbit neocortex. Calcium influx produced by depolarizing concentrations (69 mM) of K^+ was inhibited 7% to 63% by phenytoin, phenobarbital, or procaine, whereas ethosuximide was ineffective. Decreased Ca^{2+} influx was observed with as little as 0.08 mM phenytoin and 0.04 mM phenobarbital. In contrast, 4 mM procaine was needed to produce an effect. These results lead to the conclusion that ability to produce membrane stabilization is not a property of all anticonvulsant drugs; however, this property may be essential for the action of drugs effective in the treatment of major seizures.

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Phenytoin inhibits the uptake of Ca^{2+} by isolated presynaptic endings from rat brain[1] and by brain slices.[2] Barbiturates have a similar effect in synaptosomes[3] and inhibit Ca^{2+} uptake by stimulated autonomic ganglia.[4] Inhibition of Ca^{2+} uptake at nerve terminals with resulting impairment of neurotransmitter release is a mechanism that might account for the ability of a drug to suppress seizures. It is well known that both phenytoin and phenobarbital are effective in the treatment of major seizures. It is important to know whether or not the ability to inhibit transmembranous Ca^{2+} flux is a selective property of drugs effective in the treatment of major motor seizures or is also a property of agents useful in the treatment of petit mal seizures. To determine this, we have studied the action of several anticonvulsants and other drugs on uptake of ionized calcium chloride by synaptosomes isolated from rabbit neocortex. This report describes the effects of phenytoin, phenobarbital, ethosuximide, and procaine hydrochloride.

MATERIALS AND METHODS

Female albino rabbits weighing between 2 and 4 kg were killed by rapid intravenous injection of 50 ml of air. The brain was rapidly removed and placed in ice-cold sucrose (0.32M). Slices of neocortex were dissected free of underlying white matter and homogenized in ten volumes of 0.32M sucrose. Tissue from one rabbit was used for each experiment. Subcellular fractions were prepared by the method of Gray and Whittaker.[5]

Calcium uptake by synaptosomes was determined by the method of Blaustein and Weismann,[6] with some minor modifications. The synaptosome-enriched fraction was removed from the sucrose gradient, and six volumes of an ice-cold solution (solution 1) containing 132 mM NaCl, 5 mM KCl, 1.2 mM $MgCl_2$, 1.2 mM NaH_2PO_4, 10 mM glucose, and 20 mM tris (hydromethyl) amino-methane, pH 7.4, were added over a 30-minute period. The suspension was centrifuged at 11,000 g for five minutes. The pellet was suspended in a buffer similar to solution 1 but contained 1.2 mM $CaCl_2$ (solution 2). This suspension was incubated at 30 C for 15 minutes to allow ionic equilibration. In the drug experiments, aliquots were removed and mixed with solutions containing various concentrations of phenobarbital, procaine hydrochloride, ethosuximide, and phenytoin. All drug dilutions were in deionized water with the exception of phenytoin, which was dissolved and diluted in 10 mM NaOH. Aliquots of drug-synaptosome mixtures were incubated at 30 C for 15 minutes. Following this, equal volumes of

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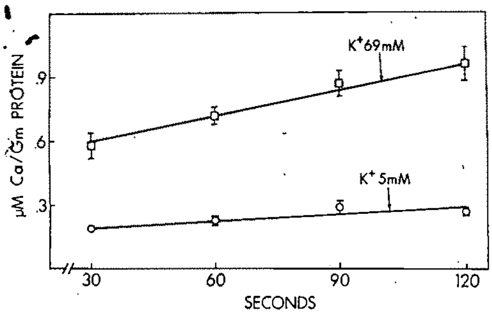


Fig 1.—Time course. Uptake of Ca^{2+} by synaptosomes, micromols per gram of protein, is shown during a two-minute period. External K^+ was present at 5 mM or at 69 mM. Each value is mean of three determinations ± standard error of the mean. No standard error indicated if it is smaller than the symbol.

solution 2 or a similar solution in which all Na^+ was replaced by K^+ was added. The added solution contained the same concentration of drug as did the synaptosome mixture to which it was added and Ca 45, 2 microcuries/ml. Synaptosome-drug suspensions plus Ca 45 were incubated for one minute at 30 C. Calcium uptake was stopped by the addition of 4 ml of ice-cold solution 1 containing 3 mM ethylene glycol bis (β-aminoethyl ether) N,N′ tetraacetic acid (EGTA). In the time course experi-

Comparisons of Efficacy of Drugs*

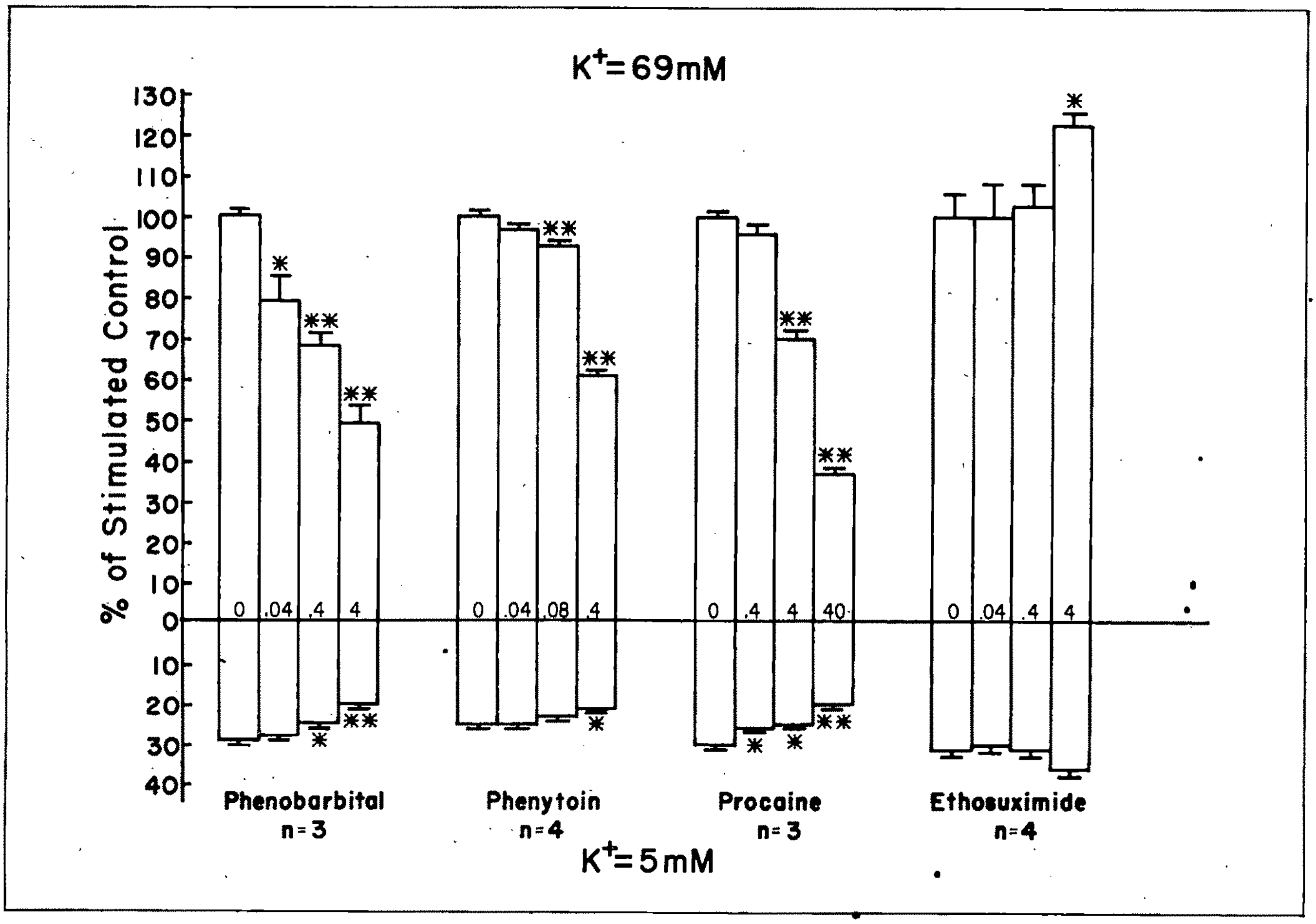
Drug	Inhibition of Ca^{2+} Uptake, μg/ml (mM)	Modification of Maximal Electroshock Seizures, μg/ml (mM)	Clinically Effective Blood Levels, μg/ml (mM)
Phenytoin†	20 (0.08)	23 (0.09)[20]	10-20 (0.04-0.08)[24]
Phenobarbital†	9 (0.04)	5 (0.02)[21,22]	9-28 (0.04-0.12)[25]
Ethosuximide‡	. . .	2,700 (19.0)[19,23]	40—80 (0.28-0.56)[26]

* Compares concentrations of phenytoin, phenobarbital, and ethosuximide effective in substantially blocking synaptosomal calcium uptake, eliminating the tonic extensor component of maximal electroshock seizures, and in the treatment of clinical epilepsy.

† Values for phenytoin and phenobarbital are those effective in treating major seizures.

‡ Values for ethosuximide are those effective for petit mal seizures.

Fig 2.—Effect of phenobarbital, phenytoin, procaine hydrochloride, and ethosuximide on Ca^{2+} uptake by synaptosomes. Each bar represents mean ± standard error of the mean of three or four determinations, as indicated. Bars above horizontal line are values determined in depolarized synaptosomes and those below line, in undepolarized synaptosomes. Numbers on bars represent drug concentrations in millimols per liter. One asterisk indicates significance at $P < .05$; two asterisks, significance at $P < .01$ (t test).



ment, drug-free synaptosomes were mixed with the drug-free solutions containing Ca 45 for varying periods of time. Uptake of Ca^{2+} was terminated, as in the drug experiments. The samples were centrifuged at 11,000 g for five minutes at 0 C and were washed twice with 4 ml of solution 2. The pellets were frozen and stored.

After thawing, the pellets were digested in 0.7 ml of 1N NaOH at 60 C for 30 minutes, decolorized with 50μl of 30% H_2O_2 and neutralized with 0.7 ml of 1N HCl. One milliliter was diluted with 10 ml of liquid scintillation solution and counted in a liquid scintillation counter. Protein was determined by the method of Lowry et al.[7]

RESULTS

During initial experiments, we examined the kinetics of Ca 45 uptake by rabbit cerebral cortex synaptosomes in buffer containing 5 mM or 69 mM K^+. Only the rate of Ca 45 uptake between 30 and 120 seconds was studied, since we were unable to measure uptake at earlier times using the present methods. In both 5 and 69 mM K^+, synaptosomes accumulated Ca 45, but in 69 mM K^+, accumulation was three-fold larger than in 5 mM K^+ (Fig 1). Most of the influx of Ca 45 apparently occurred within 30 seconds after the isotope was added to the suspensions of synaptosomes. Between 30 and 120 minutes, synaptosomes in 5 and 69 mM K^+ continued to take up Ca 45. The rate of influx during this period was linear under both conditions; however, in the presence of 69 mM K^+, the rate was three times greater. The results observed here are similar to those in synaptosomes prepared from whole rat brain.[6]

Both phenobarbital and phenytoin inhibited Ca 45 accumulation by the synaptosomes (Fig 2). In depolarized synaptosomes (ie, those in 69 mM K^+), 0.04 mM phenobarbital, the lowest concentration tested, produced 21% inhibition of uptake. Higher concentrations of phenobarbital, 0.4 and 4.0 mM, inhibited uptake an additional 11% and 31%, respectively. Phenytoin had no effect until a concentration of 0.08 mM was reached, and this concentration only produced a 7% inhibition of Ca 45 uptake. However, 0.4 mM phenytoin inhibited Ca 45 flux into K^+-depolarized synaptosomes to a greater extent than did 0.4 mM phenobarbital. Concentrations of phenytoin greater than 0.4 mM were not studied, since at higher concentrations, it was insoluble in buffers at physiologic pH. In undepolarized synaptosomes, phenobarbital and phenytoin inhibited uptake of Ca 45 slightly, but only at drug concentrations of 0.4 mM or greater.

In contrast to the findings with phenytoin and phenobarbital, ethosuximide did not inhibit synaptosomal Ca 45 influx at any concentration up to and including 4 mM (Fig 2). In fact, this drug, at a concentration of 4 mM, produced a slight stimulation of uptake.

Inhibition of Ca 45 uptake was also produced by procaine (Fig 2). Unlike phenytoin and phenobarbital, the local anesthetic drug was only effective at concentrations of 4 mM or greater. It is important to note that the inhibition produced by 4 mM procaine was only as much as that produced by 0.4 mM phenytoin or 0.4 mM phenobarbital. We also studied the effects of a central nervous system stimulant, pentylenetetrazol, on Ca 45 uptake by synaptosomes. This drug, at concentrations of 0.04 to 4.0 mM, had no effect (data not shown).

COMMENT

These results show that phenobarbital, phenytoin, and procaine inhibit Ca^{2+} uptake by synaptosomes, whereas ethosuximide does not. Phenytoin has previously been shown to have a similar effect in synaptosomes from rat forebrain.[1] Phenytoin and procaine have similar effects in rat cerebral cortex slices[2] and in lobster walking nerves.[8] In a recent report, Blaustein and Ector[3] demonstrated that several barbiturates inhibit stimulated Ca^{2+} uptake by synaptosomes from rat brain. They observed thiopental and pentobarbital to be highly effective. In contrast to the present findings, phenobarbital produced only a small, statistically nonsignificant inhibition. To our knowledge, there has been no previous report of the effect of ethosuximide on Ca^{2+} flux in nervous tissue.

It is not known, with certainty, if the effect of phenytoin, procaine, and phenobarbital is specific for the presynaptic membrane. The synaptosome-enriched fraction used in this study contained small amounts of free mitochondria, membrane fragments, and myelin in addition to synaptosomes. Each synaptosome itself also contained at least one mitochondrion. Mitochondria accumulate calcium.[9] The fact that Ca^{2+} uptake is reduced 83% by lysis of synaptosomes prior to exposure to high concentrations of K^+ suggests that the presynaptic rather than the mitochondrial membrane is the primary site of Ca^{2+} influx. Therefore, we assume that the membrane is the primary site of action of anticonvulsant drugs on Ca^{2+} influx.

The mechanism responsible for the action of phenobarbital and phenytoin on Ca^{2+} flux in nervous tissue is incompletely understood. It is improbable that these anticonvulsants produce their effects by directly competing with Ca^{2+} at transport sites in a manner similar to that of Mg^{2+}. A more likely explanation is that they stabilize cell membranes in a manner similar to local anesthetics, as suggested by Hasbani et al,[8] thereby making the membrane less permeable to the flow of ions and perhaps other substances. Several lines of evidence indicate that these drugs can stabilize excitable nerve membranes. Phenytoin reduces the hyperirritability of nerves placed in Ca^{2+}-poor media,[10,11] inhibits sodium conductance in squid axons,[12] and inhibits sodium influx in stimulated lobster nerves.[13] Barbiturates reduce the amplitude of action potentials in frog nerves[14] and reduce K^+ and Na^+ conductances in lobster nerves.[15] Phenobarbital decreases the spontaneous firing of squid giant axons in Ca^{2+}-poor media and reduces the amplitude of action potentials conducted by squid giant axons.[10] Inhibition of transmembranous ionic flux would limit the spread of seizures in two ways. First, by limiting Na^+ conductance, the development of an action potential would be impaired. Second, inhibition of Ca^{2+} uptake at presynaptic terminals would decrease neurotransmitter secretion.

It seems likely that the ability to produce membrane stabilization is a prominent and perhaps a selective action of drugs capable of suppressing major motor seizures. The finding that procaine, a local anesthetic, inhibits Ca^{2+} flux is not inconsistent with this concept. Local anesthetics have anticonvulsant properties similar to phenytoin. They have been shown to be effective in the treatment of status epilepticus[16,17] and to modify maximal electroshock seizures but not pentylenetetrazol seizures.[18]

The concentrations of phenytoin and phenobarbital that inhibit synaptosomal Ca^{2+} uptake are close to the calculated concentrations in brain that modify maximal electroshock seizures (Table). Plasma levels in patients who are taking therapeutically effective doses of these drugs also approach the concentration that effectively inhibits Ca^{2+} uptake (Table). Ethosuximide, by comparison, is only effective on maximal electroshock seizures at highly toxic concentrations,[19] approximately ten times greater than usual therapeutic doses and five times more than the highest concentrations in this study. This is probably a nonspecific action of ethosuximide at toxic concentrations. We assume that ethosuximide does not inhibit uptake of Ca^{2+} by synaptosomes because it has little or no membrane stabilizing ability. In fact, no one has demonstrated a membrane stabilizing action of ethosuximide; however, there are few published studies of neurophysiological or neurochemical effects of ethosuximide.

The ability to stabilize cellular membranes is not an essential property of all anticonvulsant drugs, since ethosuximide does not inhibit Ca^{2+} uptake. Accordingly, other pharmacological properties must be responsible for the anticonvulsant action of certain anticonvulsant drugs. Since ethosuximide prevents petit mal seizures, one of these other properties must account for its therapeutic action.

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Ethosuximide (Zarontin) was supplied by Parke Davis and Co, Detroit. Phenobarbital (Luminal) was supplied by Winthrop Laboratories, NY.

Nonproprietary Name and Trademark of Drug

Ethosuximide—*Zarontin.*

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Late-Infantile Neuronal Ceroid-Lipofuscinosis

An Ultrastructural Study of Lymphocyte Inclusions

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• Ultrastructural study of peripheral blood from two patients with late-infantile neuronal ceroid-lipofuscinosis with curvilinear bodies, demonstrated in brain biopsies revealed curvilinear bodies in lymphocytes. These findings indicate that ultrastructural investigation of circulating lymphocytes may be useful in the diagnosis of late-infantile neuronal ceroid-lipofuscinosis and may circumvent the need for brain biopsy. Curvilinear bodies were also present in the lymphocytes of a neurologically normal younger female sibling of patient 1, who has had a single seizure, leading to speculation that she may be in the early stages of the same disease. This case suggests the possibility of early detection of this disorder and indicates the importance of screening lymphocytes of siblings of affected patients. Tubular cytoplasm inclusions were present in a high percentage of lymphocytes of the asymptomatic parents and a younger sibling of these patients.

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In recent years, the neuronal ceroid-lipofuscinoses have received considerable attention. Unlike Tay-Sachs disease in which G_{M2} ganglioside accumulates secondary to a deficiency of hexosaminidase[1] or generalized G_{M1} gangliosidosis in which a deficiency of β-galactosidase has been found,[2] this group is currently classified on clinical and morphological features, because the basic biochemical defect is not understood. To confirm the diagnosis of neuronal ceroid-lipofuscinosis, brain biopsy is often performed. The majority of cases of late-infantile neuronal ceroid-lipofuscinoses studied by electron microscopy have been found to contain cytoplasmic inclusions, termed "curvilinear bodies."[3,4] The purpose of this report is to describe the presence of curvilinear bodies in lymphocytes of two patients with late-infantile neuronal ceroid-lipofuscinosis with curvilinear bodies, demonstrated in brain biopsies. In addition, the ultrastructural studies of cytoplasmic inclusions in lymphocytes of relatives are presented.

For convenience, in this article the term "late-infantile neuronal ceroid-lipofuscinosis"[5] is used because of the acceptance of this term by many authors, though it is realized that the storage material does not have the ultrastructural appearance of classic lipofuscin granules, and its true nature is not known.

REPORT OF CASES

CASE 1.–This 4-year-old boy with no known parental consanguinity or family history of neurological disorders developed well until age 1½ years when he failed to acquire any new intellectual or motor skills. At age 3 years, he experienced his first grand mal seizure. He subsequently developed an ataxic gait. Examination at age 3¾ years indicated a mental age of 10 to 11 months on the Bayley scale of infant development. Frequent lapses of consciousness and minor motor seizures were noted. His gait was markedly ataxic. No abnormalities of visual function could be detected, but both optic disks were pale, and retinal arterioles were sparse. Subtle macular pigmentary changes were present. Reflexes were 1+ in the upper extremities and 3+ in the lower extremities, and there was a left extensor plantar response.

CASE 2.–This 5-year-old boy with no known parental consanguinity or family history of neurological disorders developed an unsteady gait by the age of 2 years. At age 4 years, he experienced the onset of generalized seizures and was admitted to a hospital where laboratory evaluation, including a pneumoencephalogram, was normal. Psychometric testing showed his intellectual function to be at the 2-year-old level. By age 4½ years, he was confined to a walker, had experienced further mental

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deterioration, loss of interest in his environment, dysphagia, and an increase in frequency of seizures, some of which were myoclonic in type. Examination at age 4 years 10 months showed a dull, drooling child, with reduced motor activity and little intelligible speech. The optic disks were atrophic. The maculae were red and ringed by dark pigment. Bifacial weakness and a decreased gag reflex were present. There was increased tone in all limbs, symmetrically hyperactive deep tendon reflexes, and bilateral ankle clonus. Plantar responses were equivocal.

Laboratory evaluation in both patients was similar. Routine blood chemistries, complete blood cell counts, urinalyses, chest and skull roentgenograms, motor nerve conduction velocities, and pneumoencephalography or cerebral angiography were normal. Electroencephalograms (EEGs) showed abundant, high-voltage, irregular delta waves with multifocal spikes and 80μv to 200μv polyphasic waves in response to photic stimulation. Average visual evoked responses (AVER) in patient 1 were 5 to 20 times larger than age norms.[6] An electroretinogram showed suppression of both A and B waves in case 1. Right frontal lobe brain biopsy was performed in both patients.

Family Histories

Family of Patient 1.—Findings from a neurologic examination were normal for the patient's 3½-year-old sister, but she had her first seizure after being followed up for six months. Her EEG showed irregular delta wave activity in the left occipital region and 75μv to 100μv polyphasic waves in response to one-per-second photic stimulation. In the AVER, waves with 50- to 150-msec latency were more than three standard deviations larger in amplitude than age norms.[6] The AVER in the patient's asymptomatic 25-year-old mother were normal.

Family of Patient 2.—The patient's 3-year-old brother was asymptomatic, and findings from neurologic examination were normal. In the AVER, waves with 50- to 150-msec latency were more than three standard deviations larger in amplitude than age norms.[6] The AVER of the patient's asymptomatic 28-year-old mother were normal.

MATERIALS AND METHODS

For light microscopy, tissues from the frontal lobe biopsy specimens of patients 1 and 2 were fixed in 4% formaldehyde and embedded in paraffin. They were stained with hematoxylin-eosin, Masson trichrome method, PAS, phosphotungstic acid hematoxylin, Luxol fast blue-hematoxylin-eosin, and the Bodian method. Frozen sections were stained with oil red O. For electron microscopy, biopsy specimens were immediately fixed in 2% glutaraldehyde adjusted to pH 7.4 with 0.1M phosphate buffer for two hours. Blocks were postfixed in 1% osmium tetroxide for one hour, dehydrated through ascending solutions of alcohol and embedded in Epon 812. One-micron-thick sections stained with toluidine blue were used for light microscopical scanning purposes. Thin sections were cut with diamond knives, stained with uranyl acetate and lead citrate, and examined with an electron microscope.

Smears of peripheral blood were made in the routine manner and stained with Wright stain. For electron microscopy, samples of 5 to 10 ml of peripheral blood were drawn from the two patients described above, the mother, father, and sister of patient 1, and the mother and brother of patient 2. Similar blood samples were collected from seven control subjects, ages 1½ through 42 years, all without a diagnosis or family history of neuronal storage diseases. Blood was drawn into heparinized tubes and processed according to the method of Anderson.[7] After centrifugation for ten minutes at 1,500 rpm, the plasma layer was removed with a pipette. Phosphate-buffered 2% glutaraldehyde was carefully layered over the sedimented cells and allowed to remain for one hour. The disk of leukocytes was then removed, cut into thin blocks, rinsed with phosphate

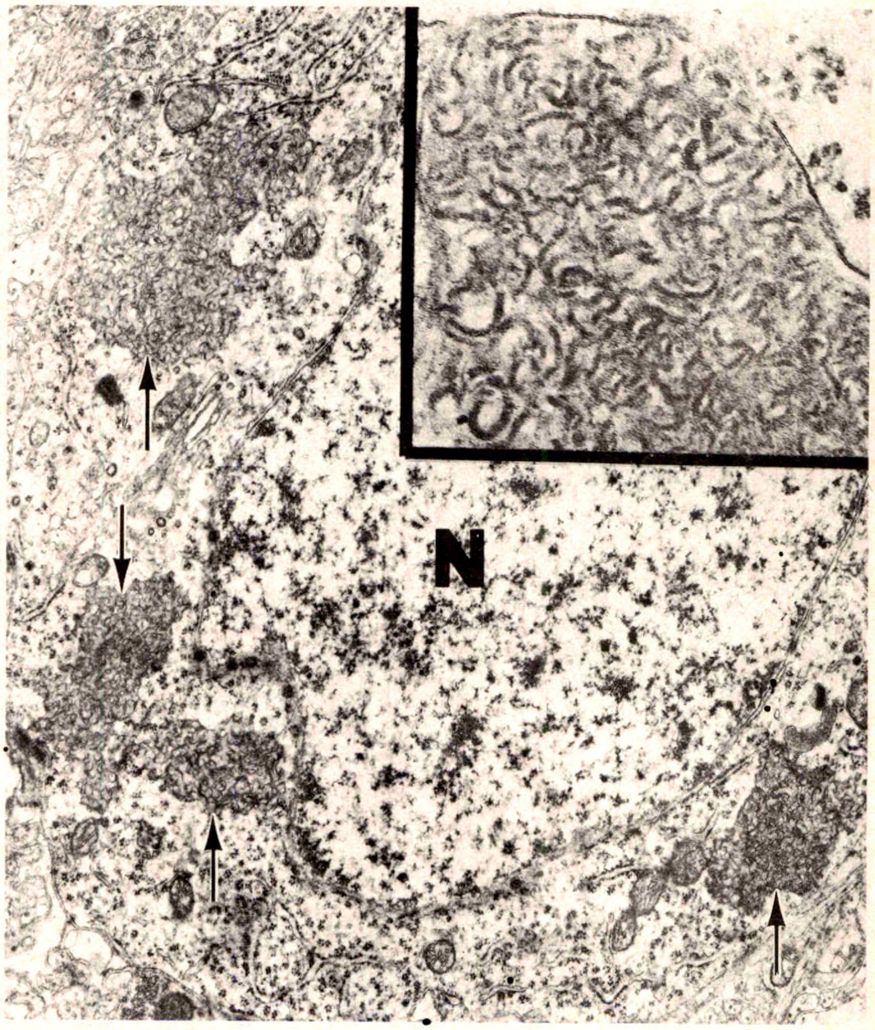


Fig 1.—Electron micrograph of cortical neuron containing four curvilinear bodies (arrows) (patient 1). N, Nucleus (original magnification ×14,200). Inset, High magnification of portion of curvilinear body from patient 2, showing individual profiles (original magnification ×86,500).

buffer, and placed in 1% osmium tetroxide for one hour. Blocks were then processed as above.

RESULTS

Cases 1 and 2

Brain Biopsy.—The findings in both cases were similar and will be described together.

Light Microscopy.—The normal architecture of the cerebral cortex was preserved, and there was no detectable loss of neurons. Many neurons demonstrated mild to moderate cytoplasmic enlargement, and some had eccentric nuclei. Their cytoplasm contained a finely granular material that was pink-red with the PAS stain and orange with the oil red O stain. An occasional neuron was shrunken, and a few neurons were undergoing disruption. Mild increases in astrocyte number and size were present in the cortex and the gyral and subcortical white matter. No other abnormalities were identified in the white matter.

Electron Microscopy.—The cytoplasm of many neurons of the cerebral cortex contained variable numbers of round, oval, or irregular-shaped cytoplasmic inclusions, termed "curvilinear bodies" (Fig 1). These inclusions often displaced other cytoplasmic organelles or completely filled the neuronal cytoplasm. They were bound by a unit membrane that was not always visible. Curvilinear bodies were composed of groups of densely packed small membranes in the shape of semicircles, circles, and wavy or curved profiles (Fig 1, inset). The individual profiles were composed of alternating electron-dense and electron-lucent lamellae of approximately equal width. The thickness of the entire profile ranged from 130 to 230 Angstrom. A few small densely osmophilic structures were present in curvilinear bodies. Curvilinear bodies were also observed in astrocytes and endothelial cells.

Peripheral Blood.—The findings in both cases were similar and will be described together.

Light Microscopy.—No detectable abnormalities were found on peripheral blood smears stained with Wright stain or on 1μ thick sections of plastic embedded leukocytes.

Electron Microscopy.—Many lym-

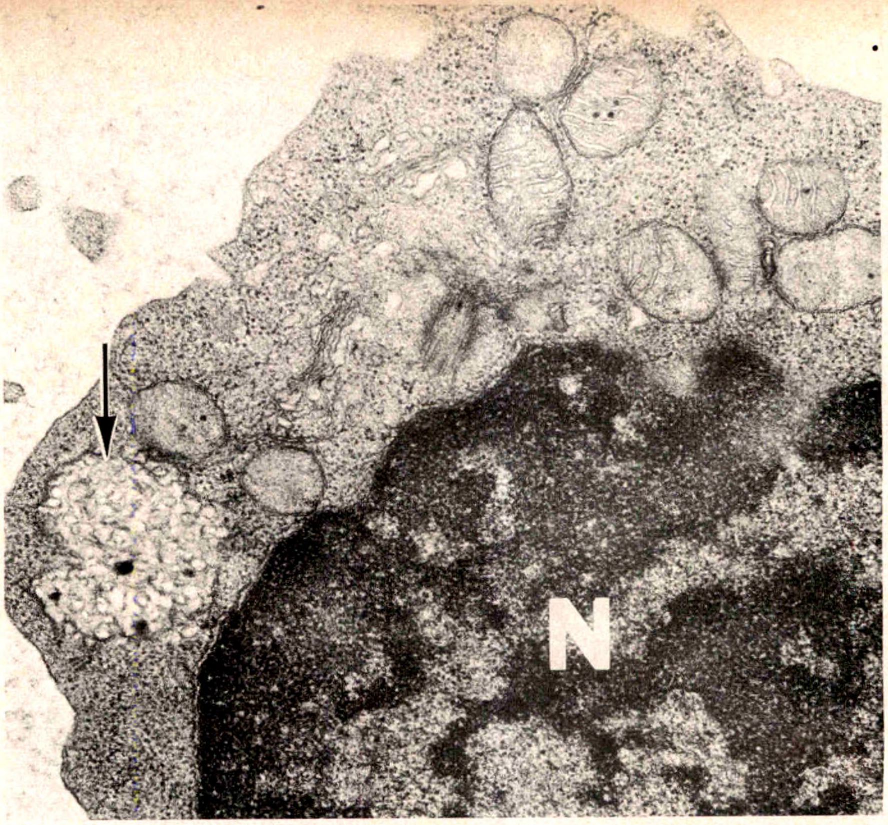
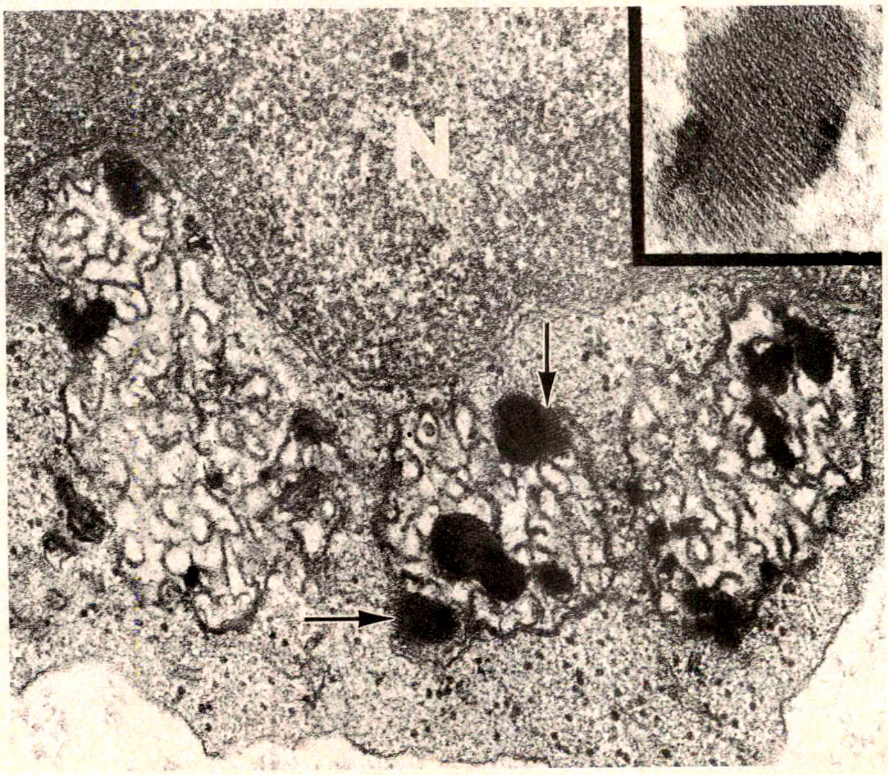


Fig 2.—Electron micrograph of circulating lymphocyte showing single curvilinear body (arrow) (patient 2). Note mitochondria, centriole, and Golgi complex in upper portion of micrograph. N, Nucleus (original magnification ×25,600).

Fig 3.—Electron micrograph of portion of circulating lymphocyte containing three curvilinear bodies. Note numerous dense osmophilic structures in curvilinear bodies, several of which have a fingerprint pattern (arrows) (patient 1). N, Nucleus (original magnification ×61,200). Inset, High magnification of similar fingerprint profile in curvilinear body from patient 2, demonstrating lamellar pattern (original magnification ×153,000).



phocytes contained single or multiple curvilinear bodies in their cytoplasm (Fig 2 and 3), with similarities to those observed in the cerebral cortex. These elements were ovoid or round in shape and varied considerably in size, though most ranged from 1μ to 3.5μ. Up to four inclusions were found in a single lymphocyte. They were bound by a single membrane that occasionally appeared densely osmophilic and thickened, possibly because of the apposition of the individual profiles of the curvilinear bodies. These profiles were composed of stacks of alternating light and dark lamellae that measured 110 to 250 A in total width. The smaller inclusions contained only 10 to 15 profiles, while the larger ones contained a hundred or more. In general, they were not as densely packed as those in the brain. They were present in 29% of lymphocytes examined in case 1 and 21% in case 2. Irregularly shaped, small, densely osmophilic structures of variable size and number were frequently present within curvilinear bodies (Fig 3). At higher magnification, some of these structures were composed of groups of parallel dense lines separated by a pale line, the total width of which was about 80 to 130 A (Fig 3, inset). These structures, which have been previously referred to as fingerprint-like inclusions,[8] always appeared in association with curvilinear bodies and were not found alone. In occasional lymphocytes, small groups of circular or semicircular membranous structures similar to the individual profiles of curvilinear bodies were lying free within the cytoplasm. These structures were often adjacent to the Golgi complex. Curvilinear bodies were not found in polymorphonuclear leukocytes, basophils, eosinophils or megakaryocytes.

Family of Patient 1

Electron Microscopy.—Ultrastructural study of peripheral blood from the 3-year-old sister of patient 1 showed curvilinear bodies in lymphocytes like those described in the two cases above. They were present in 15% of lymphocytes studied and had identical structural characteristics, including occasional fingerprint bodies.

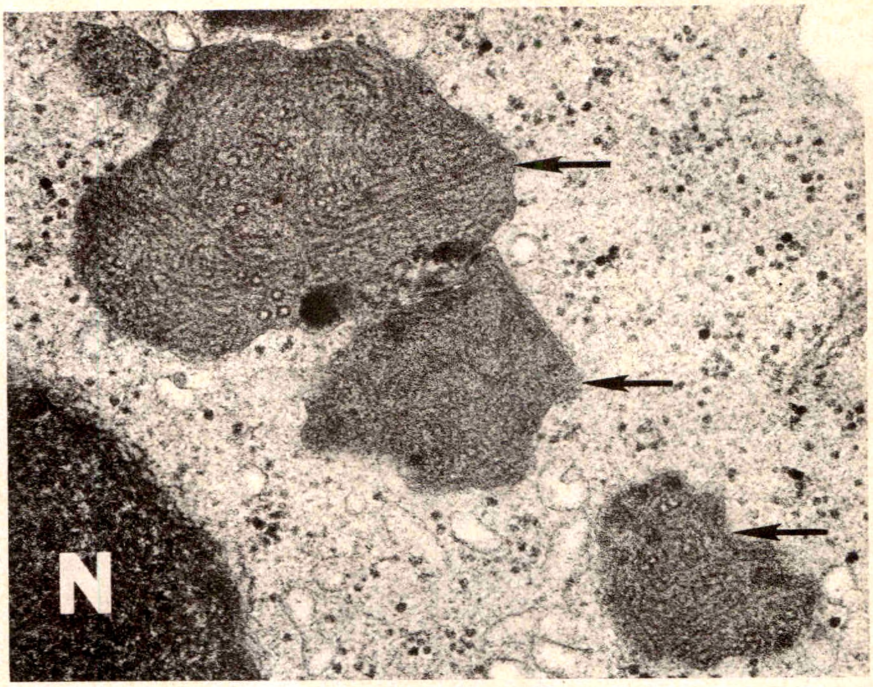


Fig 4.—Portion of lymphocyte containing three cytoplasmic tubular inclusions (arrows) (father of patient 1). N, Nucleus (original magnification ×71,200).

Study of peripheral blood of the asymptomatic 26-year-old father of patient 1 indicated numerous single or multiple lymphocytic cytoplasmic inclusions of a different character. These inclusions were composed of bundles of closely packed tubule-like structures (Fig 4), with a diameter that measured approximately 250 to 350 A and with a wall thickness of 60 to 70 A. When viewed longitudinally, they were often parallel, but occasionally had a coiled distribution. When sectioned transversely, their center was clear. A single unit membrane usually surrounded these inclusions. They were present in 28% of lymphocytes examined.

Lymphocytes of the mother of patient 1 contained similar cytoplasmic inclusions. They occurred in 18% of lymphocytes. These inclusions occasionally were in membrane-bound vacuoles and the individual tubules were less closely packed, though their ultrastructural dimensions were the same. Curvilinear bodies were not found in the mother or father.

Family of Patient 2

Electron Microscopy.—Tubular inclusions like those described in the family of patient 1 were found in 13% of lymphocytes of the mother and 9% of lymphocytes of the brother of patient 2. Curvilinear bodies were not found in lymphocytes of either of these individuals.

Controls

Curvilinear bodies were not found in lymphocytes of control subjects. Tubular inclusions were found in 1% to 6% of lymphocytes from six of seven control subjects.

COMMENT

The clinical[9] and electrophysiological[10] features found in our two patients were consistent with the diagnosis of a late-infantile form of neuronal storage disease. Brain biopsy showed PAS-positive and oil-red-O-positive material in neurons that, by electron microscopy, were found to be curvilinear bodies. Thus, this disorder conforms to the entity variously described as late-infantile ceroid-lipofuscinosis[9] or late-infantile neurovisceral storage disease with curvilinear bodies[11] or Jansky-Bielschowsky disease. A number of cases of late-infantile ceroid-lipofuscinosis with curvilinear bodies have been described, and a variety of terms have been used to describe the curvilinear bodies; eg, "multiloculated lipid bodies,"[12] "granular osmophilic deposits with membrane fragments,"[13] "aggregates of smooth membranes,"[14] "multilamellar cytosomes,"[15,16] "membranous bodies,"[17] and "cytosomes with curvilinear profiles."[18] It is clear from the ultrastructural appearance and description given that these authors are all describing the same cytosome. Curvilinear bodies have been observed in neurons, astrocytes, and perivascular cells in the brain,[3,11,15] in numerous other body organs,[11,18-21] and most recently in urinary sediment.[22] They are not exclusive to late-infantile neuronal ceroid-lipofuscinosis and have been found in the brains of juvenile-onset neuronal ceroid-lipofuscinosis.[12,17,23,24]

Numerous studies of peripheral blood leukocytes in neuronal storage diseases have been performed. Vacuoles in lymphocytes have long been observed in patients with Niemann-Pick disease,[25] Tay-Sachs disease,[26] the mucopolysaccharidoses,[27] Wolman disease,[28] and G_{M1} gangliosidosis.[29] The vacuoles in Niemann-Pick disease have been identified by electron microscopy as lipid cytosomes by Lazarus et al[30] who found them in monocytes, immature eosinophils, and platelets, in addition to lymphocytes. Ultrastructurally, those in G_{M1} gangliosidosis appear to be clear lipid vacuoles.[29] Merritt et al[31] and Donahue et al[32] demonstrated azurophilic hypergranulation in neutrophils of patients with Batten disease. Lamellar and tubular cytoplasmic inclusions in lymphocytes have been recently reported in two patients with late-onset amaurotic idiocy and their parents.[33,34] More recently, another report described curvilinear cytosomes, fingerprint bodies, and membranous and tubular inclusions in lymphocytes of patients with late-infantile and juvenile-onset ceroid-lipofuscinosis.[35]

No abnormalities were detected by light microscopical studies of peripheral lymphocytes from our two patients with late-infantile ceroid-lipofuscinosis in whom curvilinear bodies were found in lymphocytes by electron microscopy. The similarities of the ultrastructural characteristics of curvilinear bodies in the brain and lymphocytes establish the fact that we are dealing with the same basic structures. These inclusions were not observed in lymphocytes from normal control subjects. Thus, our studies indicate that it is possible to contribute to the diagnosis of late-infantile neuronal ceroid-lipofuscinosis by electron microscopical study of lymphocytes in patients with clinical and electrophysiological manifestations of the disease. The presence of curvilinear bodies in a readily accessible tissue, such as blood, and the ease of their ultrastructural recognition could possibly circumvent the need for brain biopsy. It should be emphasized that confirmation of these findings in lymphocytes from other cases of late-infantile neuronal ceroid-lipofuscinosis is needed before this is a reliable and accepted method of diagnosis.

It is of considerable interest that curvilinear bodies were found in the lymphocytes of the 3½-year-old sister of patient 1. Although she was neurologically normal, her EEG and AVER were abnormal. Six months after curvilinear bodies were discovered in her lymphocytes, she experienced a seizure. It is possible that she is in the early stage of the same disease that her brother has, though this can only be determined by thorough neurologic follow-up. If this is the case, finding curvilinear bodies in lymphocytes prior to clinical symptoms of the disease would indicate that extremely early detection may be possible using this approach. It would also emphasize the importance of screening lymphocytes of all siblings of affected patients by electron microscopy. Another possible explanation of our findings is that she is a heterozygote carrier of this genetic marker. If this is subsequently proved to be the case, it may have considerable genetic application.

The tubular inclusions found in the unaffected members of the families of both patients are also of interest. These cytosomes varied in size, but most were relatively small, and high-magnification scanning was required to detect their true configuration. Comparable lamellar and tubular inclusions have been described in the lymphocytes of two patients with "late-onset amaurotic idiocy" and their neurologically normal parents,[33,34] in the lymphocytes of the parents of two patients with late-infantile ceroid-lipofuscinosis with curvilinear bodies, and in a patient with juvenile-onset ceroid-lipofuscinosis.[35] Tubular inclusions also have been observed in lymphocytes from patients with Niemann-Pick disease[30] and in lymphocytes from a patient with rheumatoid arthritis.[36] Structures with some similarities have been found in renal and skin endothelial cells and leukocytes of patients with collagen diseases,[37,38] but not in controls. Whether those are the same structures we have observed is not known. Several authors have described tubular inclusions in lymphocytes of healthy persons.[39,40] We found them in a small percentage of lymphocytes of six of seven control subjects. Though the cytoplasmic tubular inclusions described in the above studies differ slightly in configuration and in dimension of the individual tubules, it does appear that they are not specific for any one disease and that they are present in a small percentage of lymphocytes of some normal people. Their presence in such a high percentage of lymphocytes in unaffected members of the families of our patients could possibly have some genetic significance, though this remains to be determined. A search for their presence in other members of families of patients with neuronal ceroid-lipofuscinosis, as well as other disease states and large numbers of control subjects, is needed to answer this question.

The presence of small numbers of fingerprint profiles within curvilinear bodies in lymphocytes of both of our patients and the sister of patient 1 is of interest. Fingerprint cytoplasmic inclusions are commonly found in the brains of patients with juvenile-onset neuronal ceroid-lipofuscinosis.[8,18,41,42] They also have been observed in lymphocytes in two patients with this disorder.[35] The coexistence of curvilinear bodies and finger print profiles has been reported in brain biopsy specimens of patients with neuronal ceroid-lipofuscinosis[17,18,23,33,41,42] and has been used as an argument against classifying these disorders on the basis of ultrastructural characteristics.[43] The presence of both curvilinear bodies and fingerprint bodies in lymphocytes of our patients would seem to support this position. Perhaps the presence of these structures in a readily accessible tissue, such as blood, will stimulate further biochemical studies to detect their composition and allow for classification of these disorders on a more sound basis.

Since the writing of this article further follow-up information of the sister of patient 1 indicates that she has continued to have seizures. On examination, she now exhibits a mild intention tremor of the right hand, slightly wide-based gait, and macular pigmentary changes and is presumed to have the same disease as her brother. This suggests that detection of this disorder prior to development of clinical symptoms is possible by electron microscopical study of peripheral lymphocytes.

John Heckenlively, MD, interpreted the electroretinogram. Katherine Stintz and Miranda Broyles provided technical assistance.

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Dominant Inheritance of McArdle Syndrome

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• Myophosphorylase deficiency (McArdle syndrome) is an uncommon condition characterized by exercise intolerance, muscle cramping, and myoglobinuria. Although the original report by McArdle[1] dealt with a sporadic case, subsequent cases reported in the literature show high familial incidence and consanguinity, implying that the defect is transmitted as a rare recessive gene or a possible sex-limited mode of inheritance. The present report describes the clinical, histoenzymatic, and biochemical findings in a 40-year-old woman with myophosphorylase deficiency. The family history reveals that four other members are also affected: an older sister, a younger brother, a 10-year-old son, and her 75-year-old mother, and possibly her maternal grandmother. Because of this particular pattern of direct transmission in this family, a dominant inheritance is postulated.

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In 1951 McArdle[1] reported on a 30-year-old patient with exertional cramps, exercise intolerance, and lack of normal increase of venous lactate level after ischemic exercise. He postulated a defect in anaerobic glycolysis, which was subsequently confirmed in 1959 by the simultaneous reports of Schmid et al[2] and Mommaerts et al,[3] who demonstrated absence of muscle phosphorylase. More extensive clinical and metabolic studies were reported later.[4]

The original report by McArdle[1] was of a sporadic case, but other families demonstrated autosomal recessive inheritance[5-14] with a high incidence of consanguinity.[5,7,10,14] In some of the early reported cases, the enzyme was lacking in both biochemical and immunological tests. In a second form of myophosphorylase deficiency, enzymatically inactive phosphorylase protein could be demonstrated immunologically.[15,16] We now describe a third form of this disease in a family with myophosphorylase deficiency involving at least four generations with autosomal dominant inheritance (Fig 1).

METHODS

Venous lactate generation after forearm ischemic exercise was evaluated by a modification[17] of McArdle's technique[1] with a fixed work load of 7.2 kg/meter/min. Muscle specimens obtained from open (patients 1 and 4) and needle (patients 2 and 3) biopsies were frozen immediately in liquid nitrogen and stained with hematoxylin-eosin, modified Gomori trichrome,[18] oil red 0, and PAS.[19] The following histochemical reactions were also performed: myofibrillar adenosine triphosphatase (ATPase) at pH 9.4, reduced nicotinamide-adenine dinucleotide tetrazolium reductase (NADH-TR), and phosphorylase A and B.[20,21] Biochemical analyses of muscle glycogen,[22,23] myophosphorylase B by two methods,[24,25] and phosphofructokinase[26] were performed. Concentric needle electromyography was performed on patients 1 and 2.

REPORT OF CASES

Case 1. (III-5).—The propositus, a 40-year-old school teacher of Irish-German extraction, was well in early years of life except for minor exercise intolerance that did not interfere with her daily activities. In high school she took part in physical education, but was only able to run across a basketball court once because of muscle

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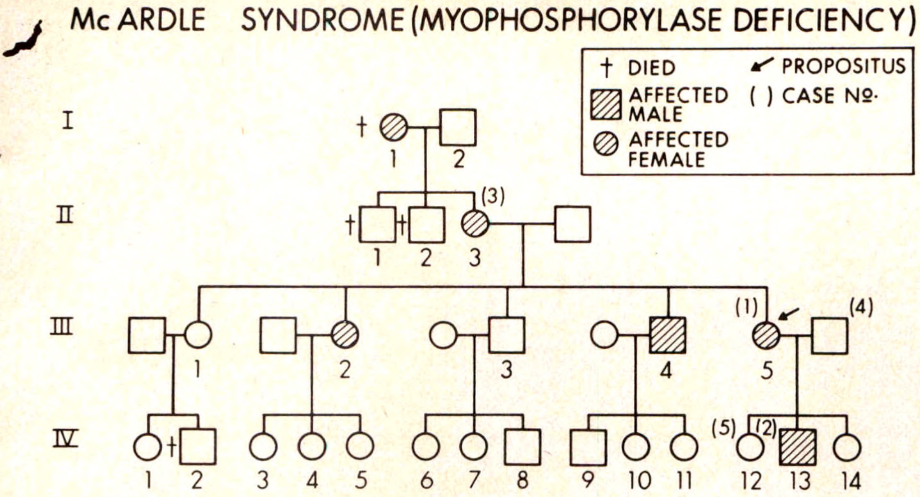

Fig 1.—Genealogy of family with autosomal dominant pattern of myophosphorylase deficiency.

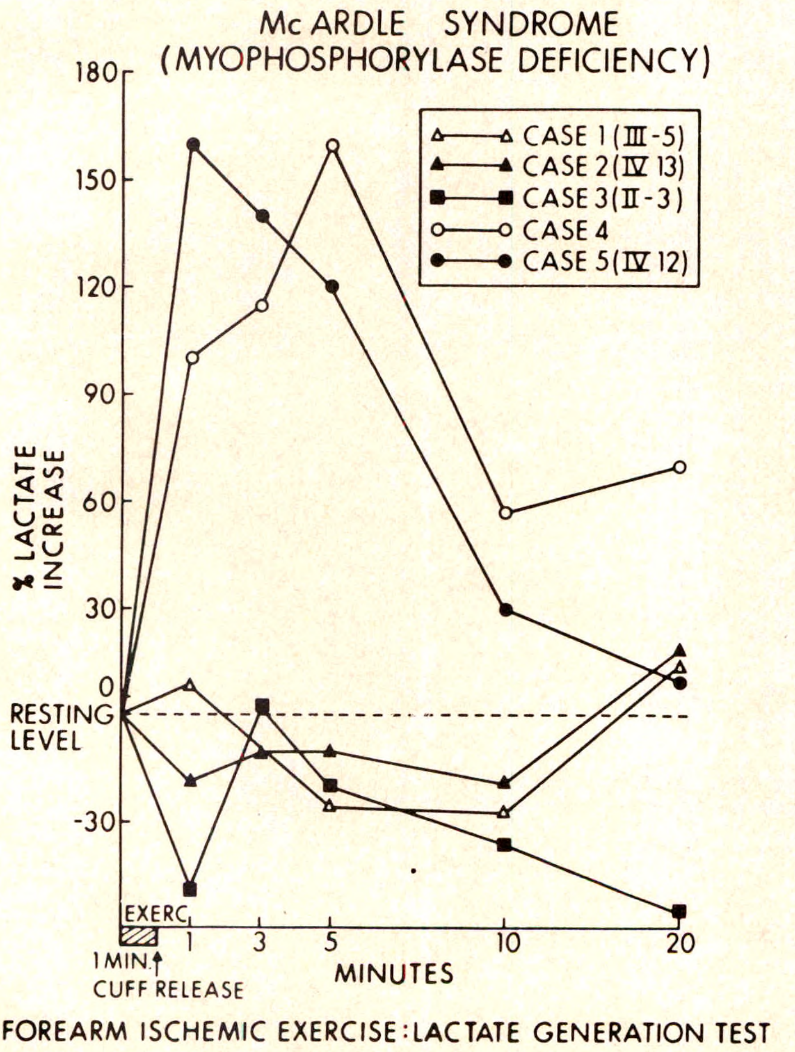

Fig 2.—Forearm ischemic exercise test shows failure to elevate lactic acid in patients 1, 2, and 3. Patients 4 and 5 show normal rise (2.6-fold, or 160% increase).

cramps and pain. On hikes, she had to stop and rest frequently because of similar symptoms. On other occasions, when walking a mile, she would experience generalized fatigue, muscle cramps, and palpitations. After one block she would stop, count to 10 or 20, and then walk another block, after which she experienced a "second wind" and could then continue walking almost indefinitely. This also occurred with bicycle riding and other activities, as long as they were done on level ground. Going up a hill, however, caused leg weakness, gastrocnemius and quadriceps cramps with painful spasms, hardening of the exercised muscles, and palpitations. After excessive work, she was able to avoid cramping by a peculiar "working out" activity. For example, if she moved a heavy couch and arm cramps developed, she could avoid severe pain by repetitively using her muscles. If she initiated entirely new activities or those that had not been performed for several months, she had considerable difficulty, but if she built up gradually over a period of weeks she was able to tolerate more. She thought that if she were able to devote more of her time to a graded exercise program she might function normally. She recognized no episodes of myoglobinuria.

Neurological Examination.—Mental status and cranial nerves were normal. There was no evidence of atrophy, fasciculations, myoedema, or myotonia. There was moderate weakness of neck flexors and minimal weakness of both deltoid muscles. After 20 or more repetitive hand grasps she experienced minor cramps and discomfort in her forearm flexor muscles. Tendon reflexes were normal and sensation was intact. The general medical examination and cardiac status were normal.

Routine Blood Studies.—Complete blood cell count, serum electrolytes, blood urea nitrogen, serum creatinine, and fasting blood glucose levels, glucose tolerance test, electrocardiogram, serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, and lactic dehydrogenase levels were normal. Creatine phosphokinase (CPK) level was 430 milli-international units (normal, 25 to 200).

Special Studies.—Forearm ischemic exercise showed no elevation of lactate level (Fig 2) after 6.36 kilogram-meters (kg-m) of work in 53 seconds. Forearm pain and flexor muscle cramps lasted four minutes.

Concentric needle electromyographic examination of the right deltoid, extensor carpi radialis, quadriceps, and tibialis anterior muscles showed no abnormalities. On separate occasions, after ischemic exercise a small concentric needle electrode was placed in the forearm flexors during a

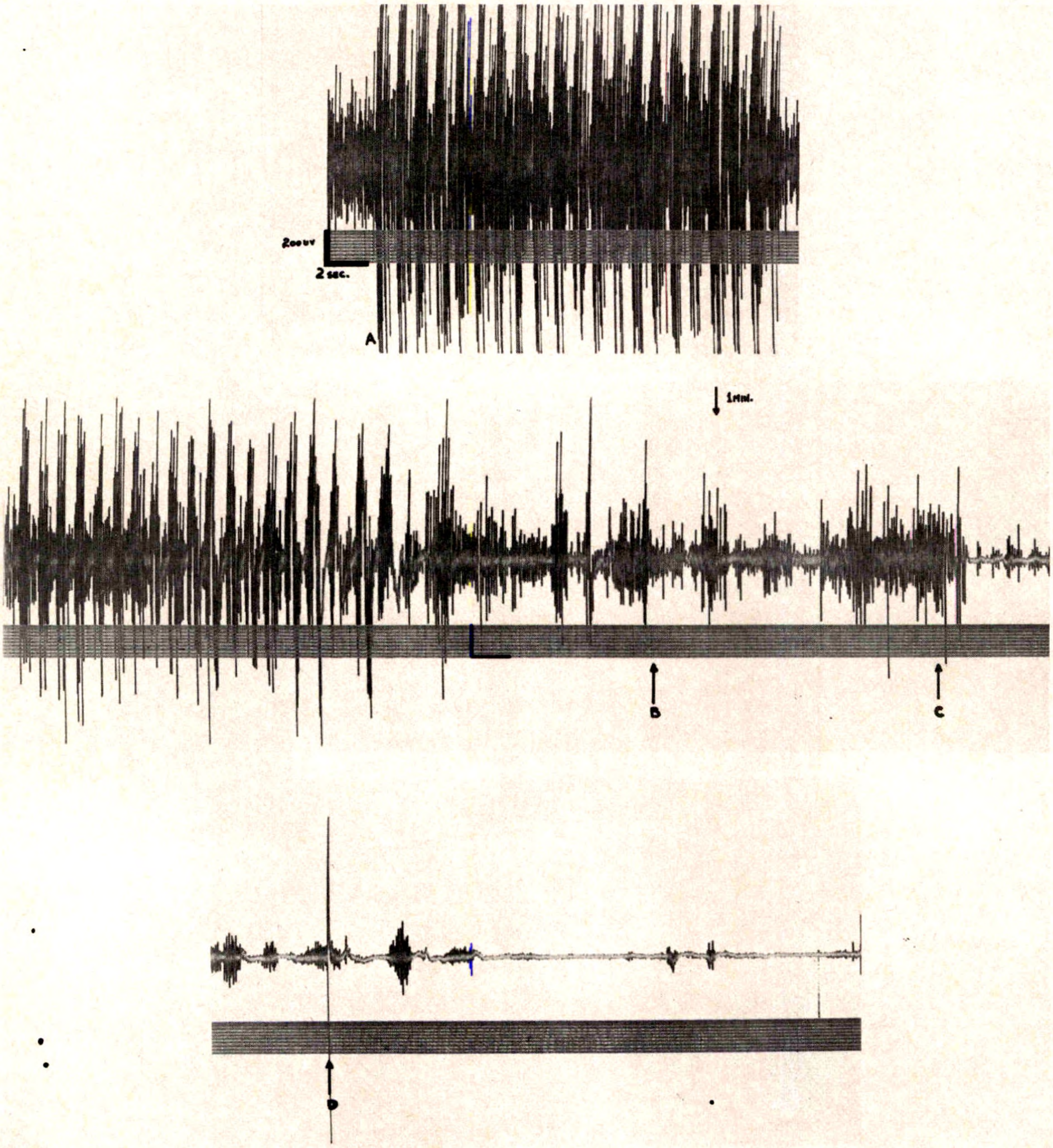

Fig 3.—Case 1 under ischemic conditions (sphyngomanometer cuff inflated to 200 mm Hg) with concentric needle electrode inserted in forearm flexors. Patient started exercise at point A. At point B, there was considerable discomfort with progressive cramping and marked shortening of muscles. At point C, exercise could no longer be carried on. From point D there is almost complete electromyographic silence.

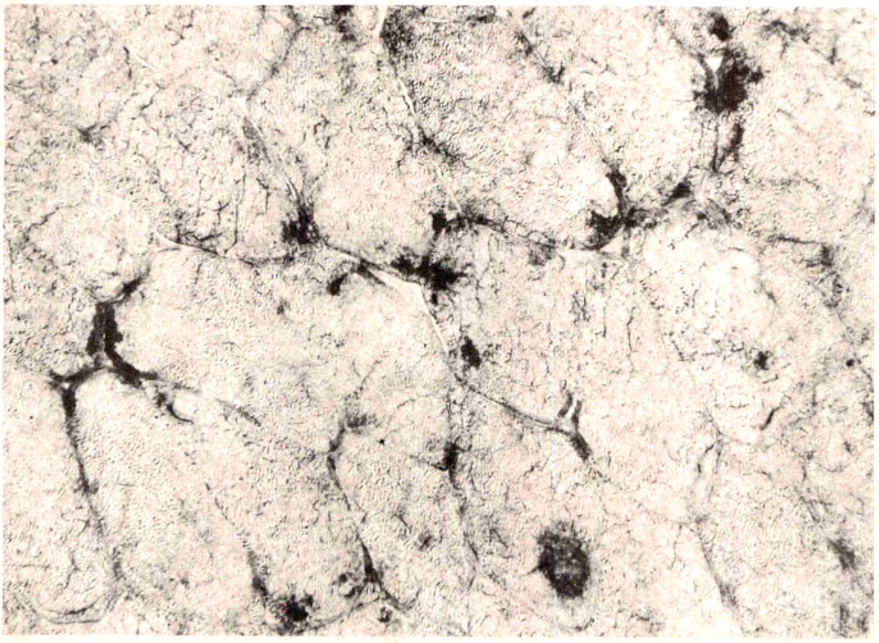

Fig 4.—Case 1. Accumulation of PAS-positive material at edges of muscle fibers (transverse cryostat section ×300).

cramp. The muscle was almost completely electrically silent (Fig 3).

Light microscopic routine stains of the muscle biopsy specimen obtained from the left vastus medialis muscle showed scattered, atrophic fibers. No vacuoles were observed. PAS stain showed increased amounts of positive staining material at the fiber edges (Fig 4). The alkaline ATPase reaction showed a normal distribution and percentage of fiber types, and NADH-TR reaction showed a normal density and distribution of reaction product. Both phosphorylase A and B activities were totally absent in all muscle fibers (Fig 5, left).

Total muscle glycogen content was 2.2 gm/100 gm net weight (normal, < 1.0 gm). Phosphorylase B activity was undetectable by both methods.[24,25] Phosphofructokinase activity was 33 μmol/min/gm (normal, 9 to 36).

Case 2 (IV-13).—The son of III-5 was born after an uncomplicated pregnancy and delivery. In his early years he tired easily, but this was not considered abnormal by his parents. At age 7, however, his parents became concerned that he had the family trait of exercise intolerance. When riding his bicycle, he was not able to keep up the pace of the normal family members and tired at about the same time as his affected mother. At age 8, while playing Little League baseball, he was unable to do endurance running and was accused of "giving up" by his coach. He was assigned to first base, which required relatively little sustained activity. He was able to hit a home run and run around three bases, but could not continue to home plate. He was never able to carry on long and sustained motor activity because he invariably experienced gastrocnemius muscle cramps. He never experienced pigmenturia.

At age 11 he was well proportioned, with normal habitus and development. Mental status and cranial nerves were normal. There was no atrophy or fasciculation. Quadriceps and gastrocnemius muscles seemed disproportionately large. There was mild weakness of the neck flexors, deltoids, tibialis anterior, and peroneal muscles. Reflexes were normal.

Routine blood studies, CPK values, and aldolase levels were normal. Venous lactate level did not increase after forearm ischemic exercise (Fig 2). He could complete only 5.76 kg-m of ischemic work in 48 seconds because of muscle cramps that lasted approximately ten minutes. During this time, electromyography revealed no electrical activity in the contracted muscles.

Electromyography of right biceps, triceps, deltoids, quadriceps, and anterior tibialis muscles at rest was normal. Needle muscle biopsy of right rectus femoris muscle showed minimal accumulations of PAS-positive material. Phosphorylase A and B activities were absent (Fig 5, right). There was a normal fiber type distribution.

Case 3 (II-3).—The mother of patient 1 was a 75-year-old retired school teacher who had had similar complaints of muscle weakness, cramps, and exercise intolerance since childhood. She also experienced the "second wind" phenomenon. There was little progression of symptoms, although because of her age she limited physical activity.

Examination was normal except for mild weakness of neck flexors, deltoids, and quadriceps muscles. No increase in venous lactate level was observed after 7.2 kg-m of ischemic work in one minute (Fig 2). She did not experience muscle cramps during the test, although she complained of moderate discomfort and fatigue at the end. A needle muscle biopsy specimen from the left rectus femoris muscle showed a normal distribution of fiber types and histochemically normal phosphorylase A and B activity.

Case 4 (III-6).—The unaffected 50-year-old husband of patient 1 was asymptomatic, and normal on examination. Forearm ischemic exercise (7.2 kg-m in one minute) produced a normal rise in serum lactate level (Fig 2). Open muscle biopsy specimens from the right biceps showed normal phosphorylase A and B activity. Phosphorylase B activity was 68 μmol/min/gm (normal, 25 to 76), and phosphofructokinase, 59μmol/min/gm (normal, 9 to 36). Glycogen content was 5.5 mg/100 gm net weight (normal, less than 1.0 gm).

Case 5 (IV-12).—The unaffected 13-year-old daughter of patient 1 was also asymptomatic and normal on examination. Lactate response to forearm ischemic exercise (7.2 kg-m in one minute) was normal (Fig 2). Muscle biopsy was not performed.

Three other family members (maternal grandmother, older brother, and sister of patient 1) were not available for evaluation. However, by history, they had similar symptoms of exercise intolerance, cramps, and "second wind." After playing a match of tennis, the older brother had one episode of pigmenturia, but details were not available.

COMMENT

Of the 47 cases of McArdle syndrome to our knowledge published through 1974, twenty-eight (59.5%) had a family history of the disorder. All familial cases were consistent with autosomal recessive inheritance. Four families had consanguineous marriages.[5,7,10,14] Of the probands, 33 were males and 14 females. This male preponderance suggests a sex-limiting factor or selective elimination of the female homozygote during gestation.

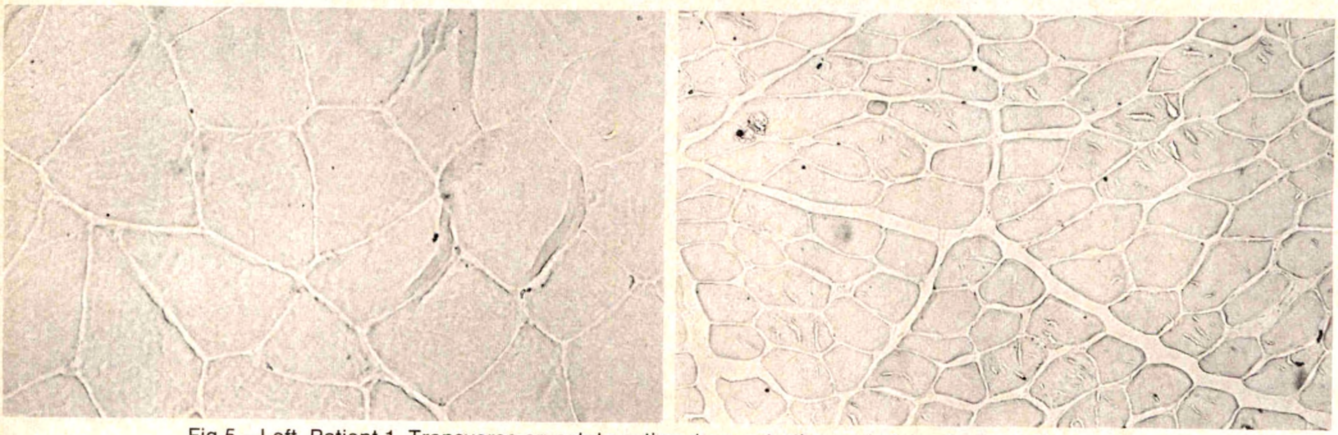

Fig 5.—Left, Patient 1. Transverse cryostat section demonstrating complete absence of myophosphorylase activity. Part of blood vessel wall shows positive reaction (myophosphorylase A reaction ×300). Right, Patient 2. Transverse cryostat section showing complete absence of myophosphorylase activity (myophosphorylase A reaction ×120).

In the family reported here, at least four consecutive generations were affected, best explained by dominant inheritance. Because this gene is rare, autosomal recessive transmission is highly improbable without consanguinity, and an extensive search of the family tree showed this not to be the case. Furthermore, the proband's husband (patient 4) had a normal rise in venous lactate level after ischemic exercise and normal phosphorylase activity, both biochemically and histochemically. Dominant transmission has not been previously recorded, although Schimrick et al[27] reported on a 46-year-old woman with McArdle syndrome whose mother had suggestive clinical symptoms; confirmatory studies were not performed. An autosomal dominant pattern in myophosphorylase deficiency suggests a new form of the disorder and contradicts the dictum that enzyme defects are caused by recessive inheritance. Another exception to this rule is porphyria.[28-30]

McArdle syndrome shows considerable clinical variability and heterogeneity.[6,27,31] Members of the family reported here showed the clinical triad of muscle weakness, exercise intolerance, and "second wind" described in most previous cases. They differed, however, in having a much more benign clinical course. Patient 3, despite advanced age and chronic symptoms, had very little clinical deficit, and during forearm ischemic exercise had no muscle cramps. This contrasts with the progressive weakness with muscle wasting in the fourth decade in some cases.[6,32] Engel et al[33] found that regenerating muscle fibers in tissue culture from patients with McArdle disease regained phosphorylase activity, suggesting that the disease may be modified or slowed by environmental factors, such as physical activity.

There is also evidence of biochemical variability. Some patients have normal muscle glycogen content[6,31,34] although myophosphorylase is absent or inactive. Glycogen degradation in these cases may be catalyzed by lysozomal enzymes such as acid maltase. In other cases, although the enzyme could not be demonstrated by biochemical techniques, the presence of enzymatically inactive enzyme was documented by immunologic-reaction with antibody to normal myophosphorylase.[15,16] In other patients,[7,35] the enzyme could not be demonstrated by histochemical, biochemical, or immunologic techniques.

If one relies solely on histochemical techniques on a single muscle biopsy, errors in diagnosis may occur. Patient 3 reported here had a typical history but normal histochemical phosphorylase A and B activity. Several other instances of the syndrome with normal (or "reduced") histochemical phosphorylase activity have been recorded.[6,12,34,36] This could be explained in several ways: (1) A reduced amount of enzyme may be present, enough to produce a histochemical reaction product but not enough to break down sufficient stored glycogen to provide energy for short-duration, high-intensity work. This possibility is suggested by two cases[6,36] in which clinical symptoms were associated with reduced levels of the enzyme as determined by quantitative biochemistry while a histochemical reaction was present. (2) A circulating enzyme inhibitor could be present that is not operative in an in vitro histochemical reaction. (3) The enzyme may be deficient in only certain muscles, or parts of one muscle. That is, sampling variability may be present. In one patient, Roelofs et al[36] found that one quadriceps muscle had one-third the normal levels of phosphorylase, while the other had none.

A simple and convenient screening test for myophosphorylase (and phosphofructokinase) deficiency is the failure of lactic acid to rise after ischemic exercise. Forty of the 47 patients reported on in the literature had this test; 37 patients (92.5%) showed a complete lack or insufficient lactic acid elevation. Only three (7.5%) patients had an apparently normal rise.[6,32,36] An accurate work load, however, was not determined in any previously reported case; without monitoring, false-positive results may appear, since work loads below 4 kg-m/min may result in a flat curve in normal individuals.[17]

Genetic, clinical, and biochemical evidence suggest at least three forms of McArdle syndrome: (1) an autosomal dominant form that is clinically benign (described here); (2) an autosomal recessive form due to an altered enzyme protein detectable immunologically but biochemically inactive; and (3) an autosomal recessive form with total absence of enzyme (biochemically and immunologically).

This study was supported in part by grants from the Muscular Distrophy Association and Public Health Service General Clinical Research Grant RR-43. Joan Higgins assisted with the histochemical preparations, Lloyd Matlovsky assisted with the microphotography, and Robert Layzer, MD, performed biochemical analyses of muscle glycogen, myophosphorylase B, and phosphofructokinase. Marlene Stein provided secretarial assistance. Patients 1 and 2 were referred by David A. Johnson, MD.

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CORRECTION

By-lines Omitted.—In the article, "Cranial Pneumatocele—A Clue to the Diagnosis of Occult Epidural Abscess," published in the May Archives (33:372-373, 1976), the names of two of the authors were omitted.

The signature for the article should have read as follows: **G. Franklin, MD,** Department of Neurology, **K. Neilson, MD,** Department of Neurosurgery, **J. Diehl, MD,** Department of Radiology, Southwestern Medical School, University of Texas Health Science Center at Dallas, Dallas, TX 75235.

Regeneration in Duchenne Muscular Dystrophy

Electromyographic Evidence

John E. Desmedt, MD, Samuel Borenstein, MD

• Eight patients with Duchenne muscular dystrophy (DMD) and seven normal children of similar age were studied with a new electromyographic method for coherent displays of potentials. Five hundred motor unit potentials (MUPs) were analyzed in 20 proximal and distal muscles representing a wide spectrum of dystrophy. The progressive MUP disintegration by dropping out of muscle fibers was documented, as well as a high incidence of spontaneous fibrillation. A total of 386 late component (LC) potentials followed the 500 MUPs at consistent latencies. No LC occurred in normal children. The LCs result from motor axon sprouts innervating muscle fibers that are newly formed either by segmentation of existing muscle fibers (focal necrosis and membrane repair) or by muscle regeneration. Axons in DMD can thus collaterally innervate additional muscle fibers. These processes must delay the onset and progression of clinical weakness in DMD patients. •

(*Arch Neurol* 33:642-650, 1976)

Current discussions on Duchenne muscular dystrophy (DMD) emphasize the relentless deterioration of muscles with necrosis and active degeneration of muscle fibers.[1-5] Pearson found focal necrosis in young DMD children in infancy.[2,6] In early stages, areas of basophilic sarcoplasm with large vesicular nuclei and prominent nucleoli provide evidence of regeneration.[2,3,6-8] Not much has been made of the latter finding in discussions of DMD pathogenesis, because the incidence and functional significance of muscle regeneration was uncertain.

Electromyography (EMG) has hitherto been confined to an ancillary role as a diagnostic aid for documenting myopathic lesions.[9-13] Improvements in EMG now afford a more consistent analysis of motor unit potentials (MUPs) by using MUP-triggered oscilloscope sweeps and a delay line. Small and previously overlooked, but consistent, component potentials occur up to approximately 50 msec after the main MUP.[14] Such late components (LCs) are absent or rare in normal muscles, but numerous in spinal muscle atrophy or after incomplete nerve lesions, and they seem to identify muscle fibers recently reinnervated by collateral sprouts of the motor axon.[14,15] Systematic EMG analysis of DMD patients showed a high incidence of MUPs with LCs which must also be related to collateral innervation of newly formed muscle fibers.[15,16] This suggests a potential for functionally significant regeneration in DMD. We now examine this problem in detail and report the analysis of 500 MUPs in DMD muscles at various stages of the disease.

SUBJECTS AND METHODS

Eight boys, 7 to 15 years old, with typical symptoms and signs of DMD were submitted to EMG. The same methods were applied to seven normal boys, 7 to 13 years old, with normal strength and no evidence of neurological disease. The subjects received no sedation nor any drug, and their parents gave informed consent. The procedures were benign, and the only problem was to encourage the minimal sustained voluntary contractions necessary to isolate a sufficient number of MUPs. Each muscle was explored for about 45 minutes at many different sites, and several sessions were sometimes necessary.

The patients lay on a couch in a copper-shielded, warm (25 C), quiet room. A standard concentric needle electrode of 0.45 mm in diameter, with a core of 0.07 sq mm of contact surface, was used in connection with a differential high-input impedance amplifier. Muscle potential records were

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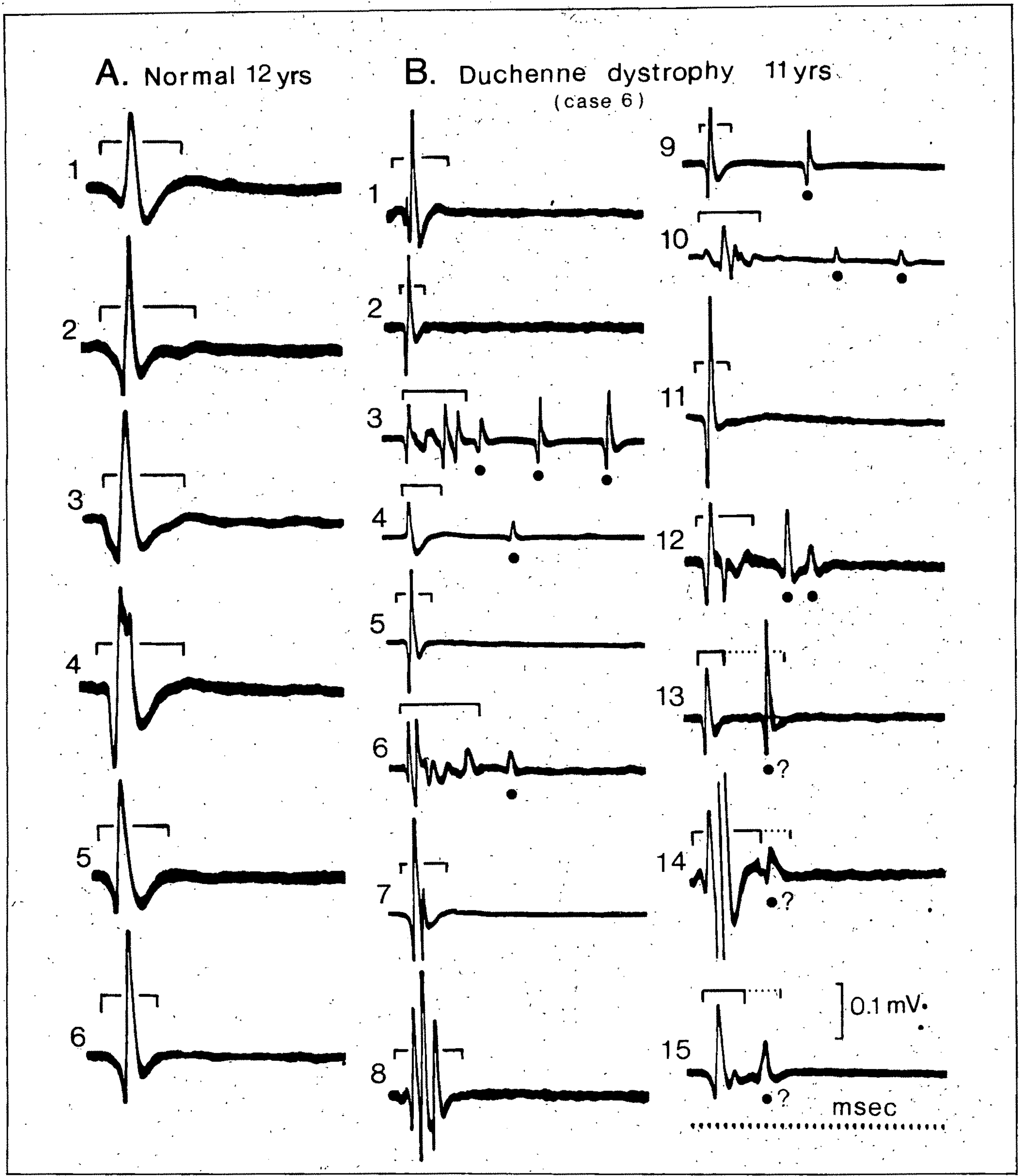

Fig. 1.—Examples of motor unit potentials (MUPs) recorded in deltoid muscles of normal child, aged 12 years, (A) and of patient 6 (B). Ten successive potentials of same motor unit superimposed in each record to show consistency of waveforms. Total duration of each MUP indicated by horizontal bracket above trace. Late components marked by dot under trace. Calibrations in millivolt and millisecond valid for all traces. Negativity of core of concentric electrode records upwards in all traces.

stored on tape for subsequent analysis when each MUP was made to trigger the sweep (5 msec/cm) of the double-beam cathode ray oscilloscope. A digital delay line (2- or 5-msec delay) was connected to the output of the first channel receiving the EMG signals and provided the input to the second channel on which the potentials were thus displayed completely, including the initial portion preceding the trigger point.[14] The digital delay line did not introduce any notable distortion in the potentials, and the overall bandpass of the system extended from 0.1 Hz to 5 kHz. A number of potentials of the same motor unit could be superimposed to show consistency of waveforms (Fig 1). Alternatively, the potentials could be photographed on moving 35-mm film (Fig 2), thus providing a column of transverse single sweeps (raster display). The vertical separation of the sweeps decreased as the motor unit discharged at a higher rate.

Strength was estimated clinically according to the Medical Research Council scale[17] from 5 to 0. As noticed by others,[18] there was no difficulty in rating muscles as 5 (normal strength) or from 0 (no contraction) to 3 (contraction possible against gravity). However, scale 4 was ambiguous in myopathies, since strength may be reduced, yet permit some contraction against moderate resistance. We used scale 4 for movement against only slight resistance and scale 4.5 for contraction against greater resistance, but with some weakness. The rating of dystrophic muscles was consistent with the amount of wasting (Table 1).

Nerve stimulation techniques were used for quantitative measurement of functional muscle in DMD patients and controls. The belly tendon compound EMG elicited by a single supramaximal electric pulse delivered to the motor nerve was recorded with skin electrodes from the abductor digiti quinti (shock on ulnar nerve at wrist), the flexor carpi radialis (shock on median nerve at elbow), and the deltoid (shock on its motor axons in the lower brachial plexus).[19-23] The overall functional value of the muscles was evaluated by a third test, namely, the pattern and voltage of the interference EMG pattern at full effort.[10-13]

The creatine phosphokinase (CPK) in serum was estimated at 25 C, using the reverse reaction activated by reduced glutathion, the adenosine triphosphate formed being assayed optically by the reduction of nicotinamide adenine dinucleotide phosphate.[24,25] The upper limit of normal was 50 international units (IU)/liter. The level of lactic dehydrogenase (LDH) was estimated by oxidation of nicotinamide adenine dinucleotide, and the upper limit of the normal range for LDH was 200 IU/liter.

			Deltoideus					
	Serum							
Patient/ Age, yr	CPK,* IU	LDH,† IU	Muscle Force Tested‡	Evoked Muscle Response, mV	No. of Motor Units Studied	No. of Motor Units With LCs§	Total No. of LCs	Fibrillation
1/7	2,000	2,170	4	2.5	39	16	18	−
2/7	1,655	1,620	4	2.5	30	17	21	+
3/8	1,900	2,200	3	2.0	14	9	23	+
4/9	460	900	2	1.2	34	8	8	++
5/10	650	824	3	1.0	34	10	13	+
6/11	710	765	2	1.4	47	18	19	+
7/14	770	2,060	4	3.0	51	32	58	+
8/15	625	560	2	0.8	43	12	16	++
Controls/ 7/13	<50	<200	5	8.5–14.0	177	1	1	−

* Creatine phosphokinase.
† Lactic dehydrogenase.
‡ According to Medical Research Council scale.
§ Late components.

RESULTS

Nerve Stimulation

The belly-tendon electrogram evoked by a single supramaximal indirect shock provides a quantitative estimate of the number of functional muscle fibers that are excitable by the motor nerve. The first negative component of the diphasic belly-tendon potential represents the global electrical response activated at the muscle innervation zone.[19,20] The voltage in the seven normal children, aged 7 to 13 years, was 8.5 to 14.0 mV for deltoid, 8.5 to 15.0 mV for flexor carpi radialis, and 6.0 to 13.0 mV for abductor digiti quinti. These figures are only slightly lower than those for normal adults, and the two ranges overlap.[23,26] In DMD patients, the abductor digiti quinti had belly-tendon voltages within or slightly below the normal range for age.[13] The proximal muscles gave lower voltages, which correlated with the amount of weakness and wasting (Table 1).

Serum Enzymes

The concentrations of CPK and LDH were elevated above normal range in all patients (Table 1). The highest figures occurred in the younger patients of the group.[27-29]

Concentric Needle EMG

The temperature of the tested muscles was monitored with a thermistor and maintained at 34 to 36 C by infrared heat.[30] Many different sites were explored in each muscle, searching for optimal needle position for recording single MUPs. In normal children, the EMG findings were similar to those in adults with good gradation of MUP at slight volition and no spontaneous fibrillation or other potentials at rest. The total duration of MUP ranged from 7 to 15 msec in normal children (Fig 1 and 3). As in adults,[12,13] most MUPs were triphasic, and the incidence of polyphasic MUPs (more than four peaks crossing the oscilloscope baseline) was 5.6% in deltoid and 7.3% in flexor carpi radialis.

Characteristic EMG anomalies[10-13] were found in all deltoid muscles of the DMD patients. Gradation was poor even in the most cooperative children; care and patience were required to obtain single MUPs on a sufficiently quiet background to permit accurate waveform analysis. A total of 292 motor units were studied in the dystrophic deltoids: 51% were polyphasic and 24% were abnormally brief (3 to 7 msec) (Fig 3, B). The sounds produced by such MUPs in the loudspeaker were typically higher pitched than normal. Spontaneous

Table 1.—Summary of Data in Eight Patients and Seven Controls

Flexor Carpi Radialis						Abductor Digiti V					
Muscle Force Tested‡	Evoked Muscle Response, mV	No. of Motor Units Studied	No. of Motor Units With LCs	Total No. of LCs	Fibril-lation	Muscle Force Tested‡	Evoked Muscle Response, mV	No. of Motor Units Studied	No. of Motor Units With LCs	Total No. of LCs	Fibril-lation
...	...	...	...	...	...	5	6.0	11	6	11	−
...	...	...	...	...	...	4.5	4.3	12	4	8	−
4	4.6	18	12	23	+	4.5	5.2	0	0	0	−
2	1.5	8	2	2	++	4	6.3	20	12	26	+
...	...	...	...	...	...	4.5	6.0	18	1	1	−
3	3.4	29	19	30	+	4.5	6.0	14	9	24	−
4	5.0	17	8	18	+	5	7.5	26	11	29	+
2	1.5	22	15	23	−	3	4.4	13	9	15	−
5	8.5–15.0	96	0	0	−	5	6.0–13.0	31	0	0	−

fibrillation potentials were present in all DMD deltoids except case 1; they were most prominent and associated with positive sharp waves in the clinically weaker deltoids of patients 4 and 8 (Table 1). These fibrillations occurred without preceding MUP activity and persisted for at least one minute after the concentric needle had been left undisturbed, so distinguishing them from activities triggered by the mechanical irritation of needle movement. Bizarre high-frequency discharges[12,13,31,32] were also observed in the deltoids of patients 7 and 8; such discharges were given time to subside before MUPs were studied in these muscles.

Forearm and hand muscles in DMD children also presented myopathic EMG patterns, but were less severe. Characteristic myopathic MUPs were observed in all DMD muscles. The flexor carpi radialis had 69% polyphasic MUPs and 15% with duration below 7 msec. The abductor digiti quinti had 64% polyphasic MUPs and 12% with duration less than 7 msec. Thus, the overall percentage of polyphasic MUPs was higher in the distal muscle than in the deltoids, while the reverse was true for the incidence of abnormally brief MUPs, confirming the known trend for dystrophic MUPs to become first polyphasic and subsequently small and brief.[13] Fibrillations

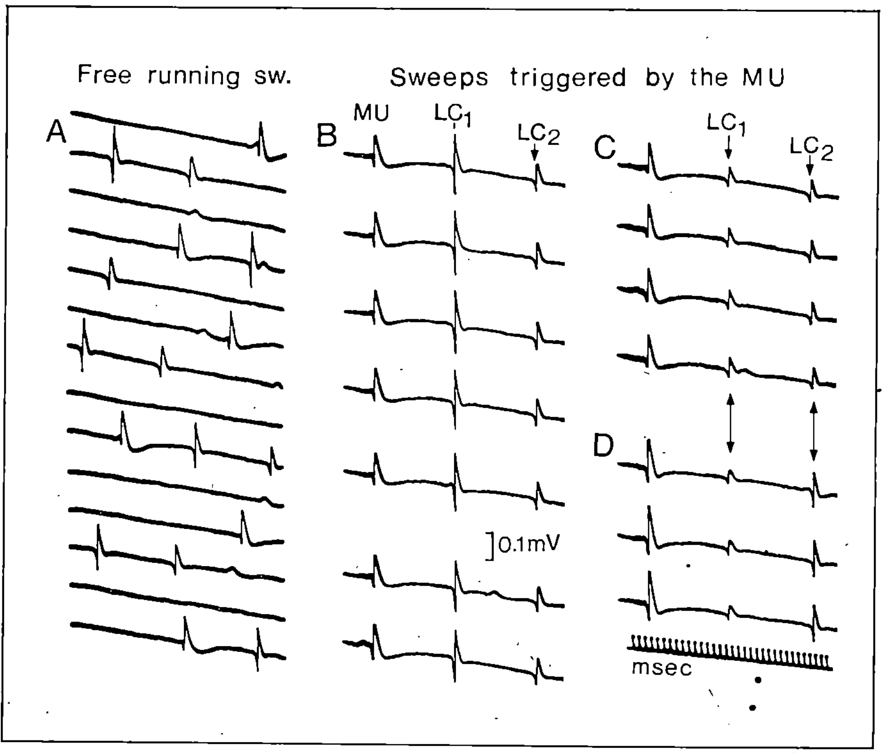

Fig 2.—Sample records of dystrophic deltoid motor unit potential (MUP) recorded in case 3. Same section of tape-recorded MUP discharge displayed on free-running oscilloscope sweeps as conventionally done (A), and also with motor unit triggered sweeps and delay line (B). Sweep speeds are same (see calibration in millisecond). Vertical spacing of traces in B corresponds to time elapsed between each discharge of MUP, whereas in A oscilloscope sweeps follow each other without interruption. Before C and D, recording electrode was slightly rotated but left at same site in muscle; this resulted in independent changes of waveforms of two late components, LC_1 and LC_2.

seemed less prominent in distal muscles, except in case 4 (Table 1). A number of bizarre high-frequency discharges were recorded in several distal muscles, particularly in patient 3.

When a muscle is voluntarily contracted at full strength, the concentric needle records an interference pattern in which the individual MUPs cannot be discriminated.[10,11] The peak-to-peak voltage of the pattern was 1.5 to 4.5 mV (mean, 2.6) in the normal children. In the DMD patients, this was reduced: 0.4 to 1.8 mV (mean, 0.9) in the deltoid and 0.6 to 3.8 mV (mean, 1.5) in the small hand muscles. The voltage reduction of the interference pattern thus showed a trend consistent with the more severe involvement of proximal muscles. However, it was a less useful measure of the severity of dystrophy in the individual muscles than the belly-tendon response to nerve stimulation, which can be more accurately measured and does not depend on the cooperation of the subject.

Late Components of the MUPs

When MUPs were observed on free-running transverse cathode ray oscilloscope sweeps, as in routine EMG, the potentials occurred at different positions on the successive sweeps since they were not synchronized with the time base electronic circuit. Limitations of this technique appear in the sample traces from a dystrophic deltoid (Fig 2, A), which would wrongly suggest three different MUPs of short duration. However, in the new method, the EMG data recorded on magnetic tape were played back with the oscilloscope time base being triggered by the MUP. A digital delay line was used to insure the display of the initial part of the MUP, which precedes the trigger point.[14-16] The alignment of the MUPs on the successive sweeps made it obvious that the three potentials were elicited by a common mechanism at fairly constant intervals: late component 1 (LC_1) arrived 13.2 msec and LC_2 19.7 msec after the beginning of the main MUP. The LC potentials were not mere repetition of the MUP because the waveforms were different. Moreover, when the concentric needle was carefully rotated at the same muscle site, the relative size of LC_1 and LC_2 could be made to vary independently (Fig 2, C and D), the latencies remaining the same. This test showed that the LC potentials were generated by muscle fibers different from those making up the original motor unit and generating the main MUP. The LCs represent activities of muscle fibers collaterally innervated by sprouts from the same motor axon, which accounts for the rather long, but fixed delay between the MUP and the LC.[14,15] With this technique, LCs are easily distinguished from other potentials, either voluntary MUPs (Fig 4, A) or spontaneous fibrillations (Fig 4, B), which have no fixed time relation to the MUP chosen for triggering the sweep.

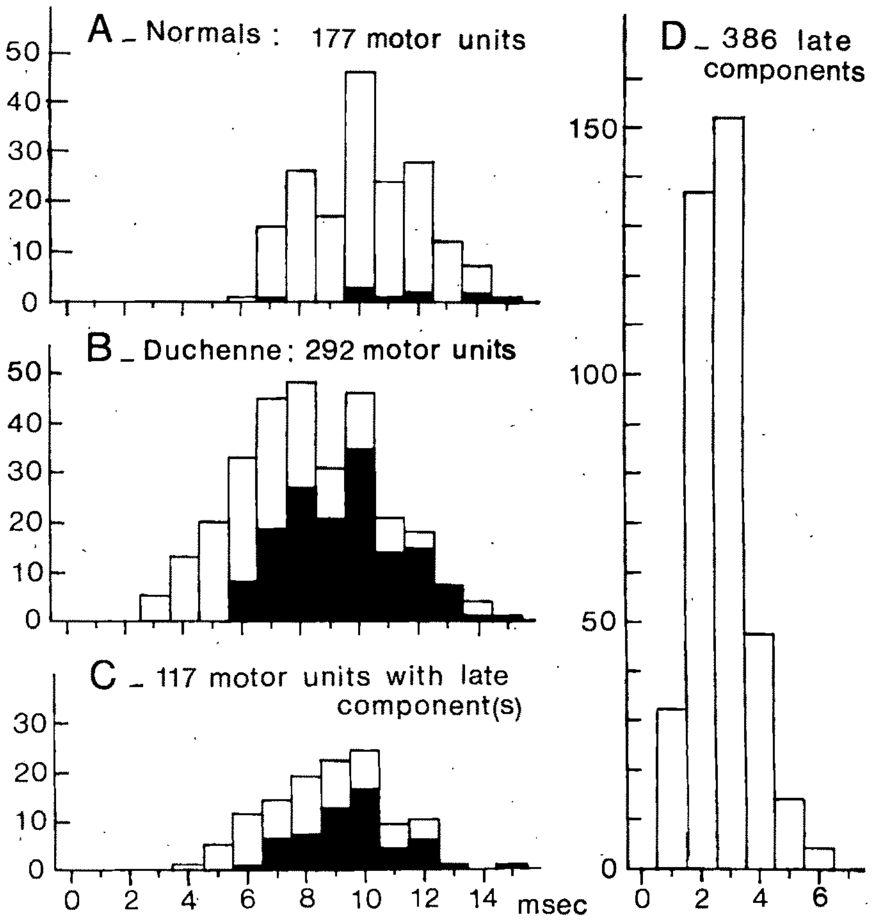

Fig 3.—Histograms of total durations of all deltoid motor unit potentials (MUPs) studied. A, 177 MUPs of seven normal children. B, 292 MUPs of eight DMD patients. Cases in black represent polyphasic MUPs. Among these 292 MUPs, 117 had one or more late components (LCs); their durations are plotted in C, with polyphasic MUPs in black. D, histogram of total durations of 386 LCs recorded in all DMD muscles studied.

Latency of LCs

Most LCs occurred between 15 and 25 msec after the beginning of the corresponding MUP, but LCs with a consistently stable latency exceeding 40 msec and up to 56 msec were also recorded (Fig 5). The lack of any preferred latency excludes spinal reflex as a possible mechanism for the LC. For the lower range of latencies, one such potential might be either a true LC or a component of the original (polyphasic) MUP. Potentials, as in Fig 1, B (No. 13 to 15) might be interpreted either way, as suggested by the dotted part of the horizontal bracket indicating MUP duration.

Several criteria can be used when evaluating such MUPs. For example, there was one blocking event of the second potential of MUP 13 in Fig 1, B, suggesting a component insecurely generated at a recently-formed neuromuscular junction (see also Fig 4, C and D). On the other hand, the occurrence of a fairly isoelectric segment of oscilloscope trace between them can suggest that the main MUP is completed before a subsequent LC arises (Fig 1, B, No. 4, 5, 9, 12).

We believe that components with consistent latencies longer than 15 msec are genuine LCs, because the total duration of MUPs (considering only unambiguous potentials) is not increased in DMD, but in fact decreases as the disease progresses (Fig 3, A and B). The components occurring between 10 and 15 msec after the start of the MUP may be difficult to interpret. Finally, components arising earlier than 10 msec after the MUP onset were not considered as possible LCs. The delays we chose are somewhat arbitrary, but they do not affect the conclusions of this study.

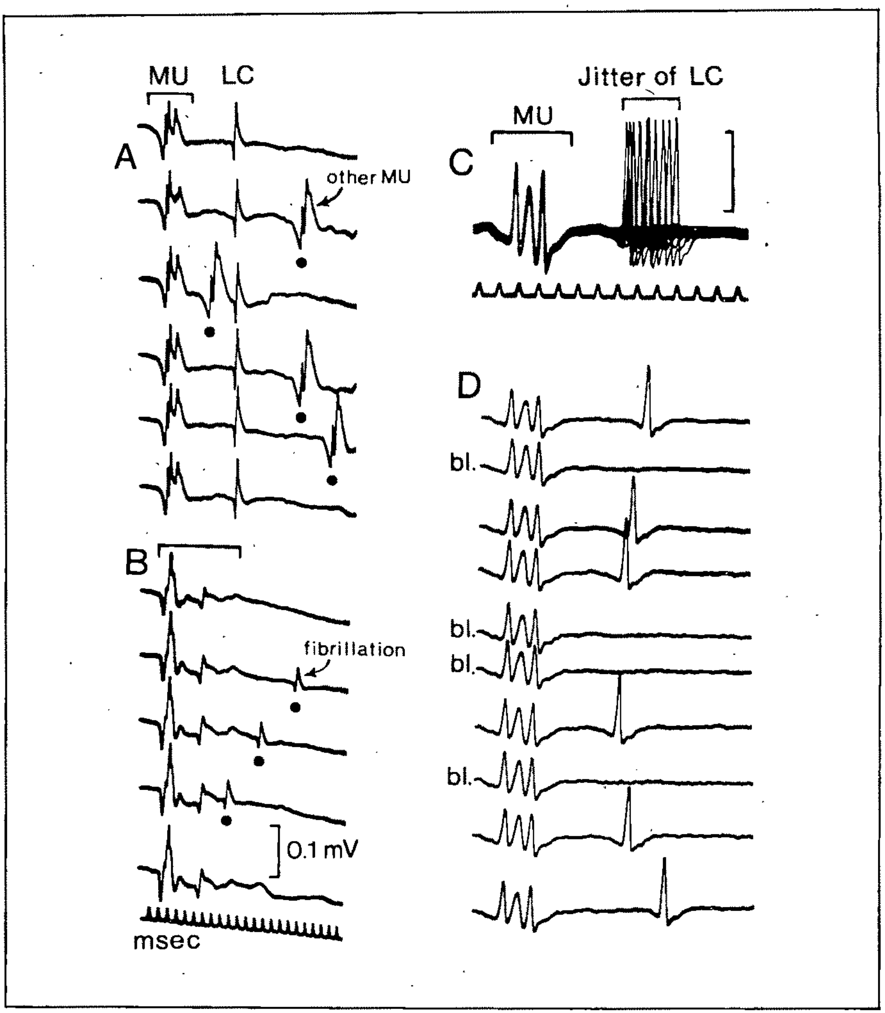

Fig 4.—Motor unit potentials (MUPs) recorded in deltoid muscle of case 5. Oscilloscope sweeps triggered by MUP. Total duration of MUPs indicated by horizontal bracket. A, polyphasic MUP with late component (LC) at stable interval; easily distinguished from discharge of another MUP (dot) that has no fixed temporal relation to MUP studied. B, another polyphasic MUP with no LC. Fibrillation potential (dot) appears with no fixed latency in three sweeps. C, brief polyphasic MUP with LC exhibiting latency jitter and blockings (several traces have no LC potential at expected time). Twenty sweeps with MUP superimposed in this record. D, samples of same MUP displayed on film moving downward to show latency jitter and blockings (bl) of LC. Vertical calibrations, 0.1 mV.

Voltage and Duration of LCs

Among the 500 MUPs studied in DMD patients, 225 had LCs of a voltage exceeding 10μV and with a consistent latency. These MUPs presented one or more LCs and sometimes as many as six. A total of 386 LCs were studied. The total duration of LCs ranged from 1 to 6 msec, with a modal value of 3 msec (Fig 3, D). Most LCs (66%) had a triphasic waveform, not unlike spontaneous fibrillation potentials with an initial positive component, a negative peak, and a third positive component (Fig 2 and 3, B). A more complex waveform with more than three phases was observed in 6% of the LCs and could correspond to subunits with several adjacent muscle fibers newly innervated by branches of a collateral nerve sprout. The peak-to-peak voltage of LCs spread over a wide range up to 600μV, but most LCs were between 20μV and 300μV (Fig 5, B). There was no statistically significant trend in the scatter diagrams relating LC latency to the total duration of the corresponding MUP or to the LC voltage (Fig 5). The LCs were about equally distributed among polyphasic and nonpolyphasic MUPs.

LC Jitter and Blockings

In muscles with a neuropathic lesion in which collateral reinnervation of muscle fibers is active,[33] many LCs may have random variations of latency over about 2 to 3 msec (jitter) as well as blockings; these features reflect the insecure neuromuscular transmission at the newly formed collateral synapses.[14,15] Similar observations were made for component fiber potentials within the MUP.[34] In DMD patients, only a few LCs showed conspicuous jitter of about 2 msec and blockings (Fig 4, C and D), but we may have overlooked significant jitters of less than 1 msec because we used a rather slow sweep speed (5 msec/cm).

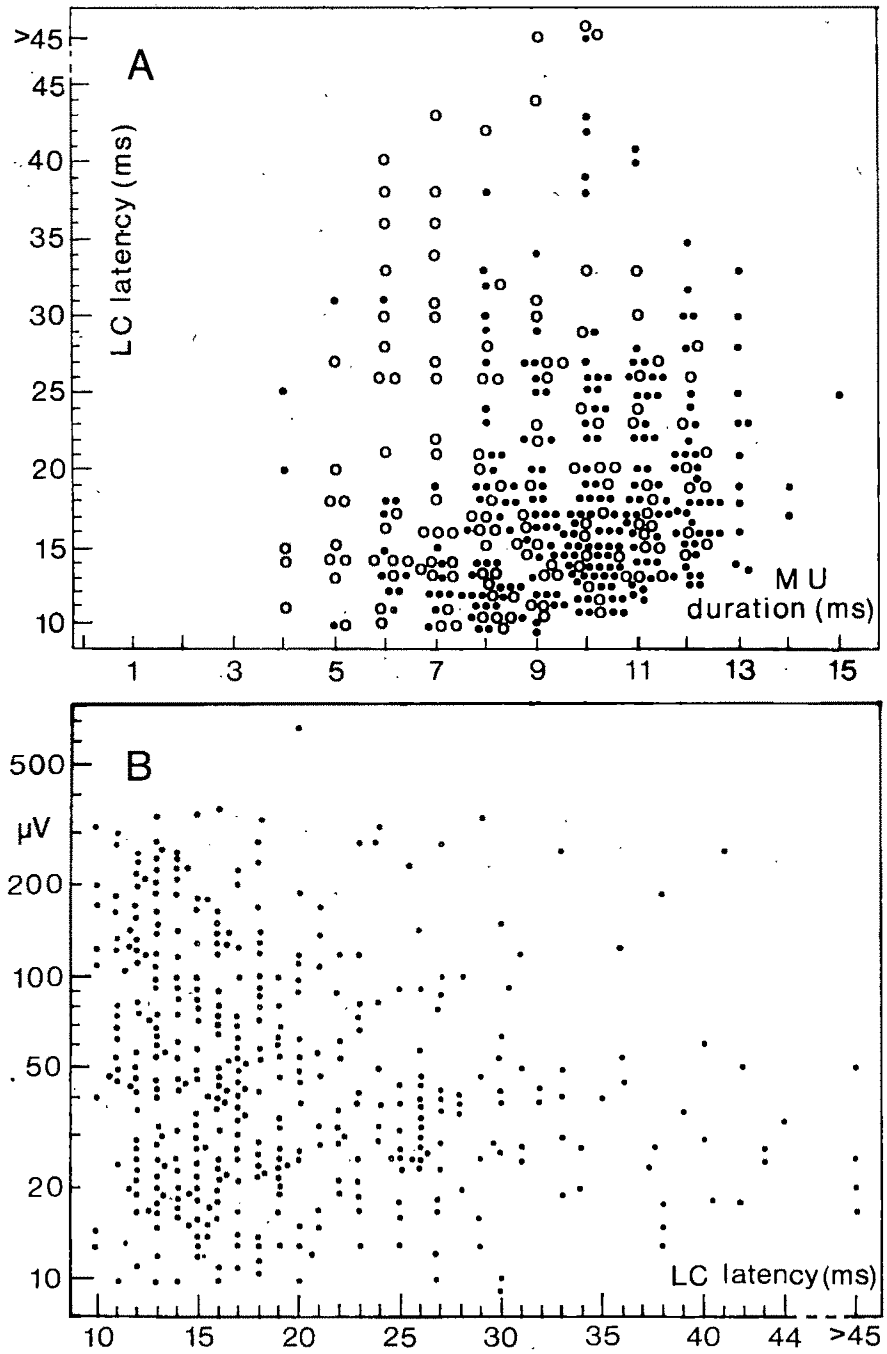

Fig 5.—Pooled data on all motor unit potentials (MUPs) with one or more late components (LCs) in all muscles studied in DMD patients. A, latency of the 386 LCs from beginning of corresponding MUP in milliseconds (ordinate) as function of total duration of MUP also in milliseconds (abscissa). Dots, polyphasic MUPs. Circles, nonpolyphasic MUPs. B, peak-to-peak voltage of 386 LCs in microvolts (ordinate) as function of their latency in milliseconds (abscissa).

Table 2.—Comparison of Late Components (LC) Latency and Voltage at Different Stages of Duchenne Muscular Dystrophy

	Cases 4 and 6		Cases 1 and 2
	Deltoideus	Abductor V	Deltoideus
No. of MUPs* studied	81	34	69
No. of MUPs with LCs, %	26	62	48
LC latency, msec	16.3	19.2	19.7
LC voltage, μV	113	98	86

* Motor unit potentials.

LCs in Normal Muscles

Muscles of normal children were investigated with the same care, but only one LC (latency, 25 msec; voltage, 165μV) was found in one deltoid muscle among 304 MUPs studied.

LCs and Stages of DMD

Table 2 compares data for the two less affected deltoids (patients 1 and 2), for two markedly involved deltoids (patients 4 and 6), and for the hand muscles of the latter patients. The incidence of LCs was less ($P < .05$) in the more affected deltoids. The LC voltage and latency were not significantly different in the three samples.

COMMENT

Only boys with unambiguous DMD were chosen from a larger population for the present study. In each case, the possibility of another diagnosis, such as spinal atrophy or nondystrophic condition, was excluded by the presence of definite myopathic EMG in the weak muscles, by the high levels of blood CPK and LDH, by the early onset of gait difficulties before the age of 3 years, and by the steady aggravation of symmetrical weakness and wasting in proximal muscles, first in lower limbs, then in upper limbs together with pseudohypertrophy of the calves. The study was restricted to proximal and distal muscles of the upper limb for several reasons: voluntary gradation of contraction is easier to obtain than in the leg; the incidence of tendon retractions and pseudohypertrophy in lower limbs introduce complicating factors; and early stages of DMD are conveniently studied in small hand muscles.[13]

Electromyographic studies have improved by using circuitry that insures coherent displays of MUPs and allows detailed visual analysis of waveform changes in conjunction with slight rotation and optimal positioning of the recording concentric electrode (Fig 1, 3, and 4). Superimposition or raster display of several samples of the same MUP removes any ambiguity about the constant features of the waveform. The true total duration of MUP, including small components, is more quickly and reliably measured. For example, considering muscles ranked according to increasing weakness in DMD (Table 1), the MUPs showed random loss of component potentials, becoming polyphasic and reduced in peak voltage, without increase in total duration (Fig 2, B). The earliest changes of MUP were readily demonstrated in small hand muscles that become weak later in the course of DMD.[13] The next stage of MUP deterioration results in notable reduction of the total duration and in small triphasic potentials representing perhaps one or only few muscle fibers (Fig 1). The classical view of dystrophic disintegration of MUPs through dropping out of component potentials[9-13] was therefore confirmed and elaborated, and is consistent with the normal numbers of spinal motoneurones in DMD autopsies[35] and with the lack of abnormality in motor axon terminals in quantitative electron microscopy.[36]

An unexpected finding was the incidence, in all DMD muscles studied, of LC potentials (Table 1). These LCs had been missed in the previous standard EMG studies, but were readily demonstrated by the coherent MUP display in conjunction with a (slow) oscilloscope sweep encompassing the entire time period when LC do occur (50 msec).[14-16] Independent changes in waveform and voltage of LC and main MUP were induced by moving the electrode; this critical test was used routinely to ascertain that any LC was genuine, not a reduplication of some MUP component, and generated by muscle fibers other than those in the MUP (Fig 3). The LCs could not be attributed to spinal reflexes, because there was no preferred latency (Fig 5), and LC latency was not longer in distal muscles. Also, some MUPs were followed by two or more LCs (Fig 1, B, No. 3, 6, 10, 12), which could not be explained by any reflex effect. The LCs are not a feature of normal muscles. Only one LC was found among 304 MUPs in normal children (Table 1).

The LC phenomenon was first discovered in patients with spinal muscular atrophy or partial nerve lesions,[14] and we have found LCs in MUPs of baboon muscles after partial experimental denervation. In these conditions, there is extensive sprouting of collaterals to reinnervate the denervated muscle fibers.[33] In partially denervated muscles, the MUPs are fewer in number, but generally of increased voltage and duration[10-12] as a result of incorporation of new muscle fibers into the original motor unit.[34] Late component latencies of 15 to 60 msec after the main MUP also suggest adoption of new muscle fibers by the motor axon, the delay of these LC potentials being presumably related to slow conduction in long, newly formed collateral axon sprouts. Neuromuscular jitter and blocking of LCs in muscles with recent partial nerve lesions accord with this interpretation and suggest insecure transmission at newly formed collateral synapses.[14,34] The LC is the electrophysiological sign of collateral innervation of available muscle fibers by a motor axon.

In DMD muscles, the high incidence of LCs associated with MUPs presenting obvious signs of myopathic alterations (Fig 1, 3, and 4) indicates that the motor axons innervating such dystrophic motor units are quite healthy and able to produce sprouts that can establish functional neuromuscular synapses with muscle fibers.[15] This is indeed in line with anatomical findings[35,36] and also with the view that the dystrophic MUPs result from random loss of muscle fibers rather than from some axonal disruption.

The major question at this stage is to identify the muscle fibers in DMD muscle that accept the collateral sprouts, most likely newly formed muscle fibers resulting from segmental necrosis, the most significant lesion in DMD.[2,3,5,8,37-39] This process may result in complete transection of a muscle fiber. Longitudinal sections of muscle biopsy specimens are rarely studied, and it has not been appreciated that necrosis only affects a very localized part of a long muscle fiber and that the segments repair surface membranes on either side of the necrotic area.[8,37-39] Segmental necrosis may transform one long muscle fiber into two short viable segments, one with the motor endplate while the other segment is deprived of motor innervation. The latter newly formed muscle fiber can thus accept innervation by a motor axon collateral. Reinnervation of endplate-free muscle segments has been demonstrated in the frog.[40] Spontaneous fibrillation potentials in DMD muscles[31,41-43] are more common than currently believed (Table 1). Segmentation of normal muscle fibers by experimental myotomy in baboon muscle is followed, after a delay of about six days, by spontaneous fibrillation.[44] The widespread segmental necrosis in DMD muscles must result in viable muscle fiber segments which fibrillate and can become innervated collaterally.[15]

Two other mechanisms may provide new muscle fibers in DMD. Longitudinal splitting of a muscle fiber into several smaller fibers occurs, but does not seem to be relevant, because the daughter fibers only separate for less than 1 mm and then recombine into a single fiber.[45] If so, splitting would not result in muscle fibers deprived of motor innervation and thus able to accept an axon collateral. Furthermore, splitting appears to be a feature of more advanced stages of DMD[45] while LCs are numerous in early stages (Tables 1 and 2). Another mechanism is de novo formation of muscle fibers from myoblasts on the surface of necrotic fibers.[2,6,8,39,46,47] Such restorative processes are most active early in DMD, but eventually become exhausted.[39] It would be important to study muscle regeneration in DMD[48] and to enquire whether drugs may promote such mechanisms.[49,50] The present evidence of functionally competent collateral innervation of new muscle fibers must delay the progression of weakness in these patients and explain why focal necrosis and signs of muscle regeneration may be seen in muscles that are not weak at preclinical stages of DMD. Segmentation of many muscle fibers must result in weakness, since shortening of the still-innervated segment would extend the other inactive segment in series and reduce the force acting on the muscle tendon. However this mechanical incompetence should be at least partially compensated through collateral innervation and neuromuscular activation of the segment previously thought to be deprived of motor innervation. If they could be influenced therapeutically, these mechanisms might permit a favorable balance between degeneration and regeneration in DMD patients.

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Clinical vs Quantitative Evaluation of Cutaneous Sensation

Peter James Dyck, MD; Peter C. O'Brien, PhD; Wilfred Bushek;
Karen F. Oviatt; Kathleen Schilling; J. Clarke Stevens, MD

• A comparison of the evaluation of cutaneous sensation by neurologic examination and by quantitative assessment in 107 patients with various neuromuscular disease has shown that there is a reasonably good correlation between the recognition of abnormalities of cutaneous sensation by clinical and by quantitative methods. Clinical neurologists tend to underestimate abnormalities of touch-pressure sensation. The quantitative evaluation of cutaneous sensation is useful in quality control of the clinical examination, in correlating the nature of sensation loss with the compound action potential and morphometry of biopsied nerve, in providing a score of sensation to follow the course and the effect of treatment protocols, and in monitoring for an adverse effect on sensation by an environmental or industrial poison. There is a good correlation between abnormality of touch-pressure sensation and loss of large myelinated fibers of sural nerve in neuropathy.

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With the development of instruments to quantitate cutaneous touch-pressure sensation,[1] thermal discrimination,[2] and pain sensations,[3] it is now possible to compare the results of such evaluation in a variety of neurologic diseases to that of the clinical assessment of cutaneous sensation. Specifically, in this study we are asking how well the clinical neurologist estimates touch-pressure sensation, thermal discrimination, and pain sensation on the hand and the foot of patients with neuromuscular disease, as compared to the determination of these sensations using quantified stimuli at specific sites for which normative values have previously been obtained.

The techniques for testing cutaneous sensation by clinical neurologists are not standardized. Neurologists do not use graded stimuli that are reproducible and quantified, and do not attempt to validate their conclusions by statistical means. This is not to say, however, that their methods do not provide meaningful results. It is part of the training of the clinical neurologist that he learn to discriminate normal and abnormal sensation from his experience with patients with and without sensory loss. Although the clinical neurologist generally does not use controls, he probably incorporates into his experience an approximation of a normal vs an abnormal response, considering site, age, sex, occupation, and level of consciousness. In some diseases that affect only a region of the body, for example one side of it, he is able to compare his findings to the unaffected (control) side. In addition, the patient may report spontaneous or stimuli-induced sensory phenomona that are typical of disturbed sensation, eg, hyperesthesia or dysesthesia may be used in recognizing abnormality apart from an elevated threshold.

There is a developing need to test cutaneous sensation with graded, reproducible, and quantifiable stimuli, utilizing the best methods of testing and scoring by comparing the results obtained in patients with neurologic disease and in suitable control subjects. Sensation laboratories using such instruments and techniques, and having normative values for site, for age, and for sex, might serve as a quality control of the clinical sensory examination. In addition, such quanti-

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tated evaluation of sensation is being correlated with the compound action potential, and with morphometry of myelinated and of unmyelinated fiber number and diameter histograms of biopsied nerve.[4] Serial evaluation of cutaneous sensation might also be used to follow more accurately the natural history of disease, and to test the effect on nerve function of various protocols of treatment. Such testing procedures might also monitor the adverse effect on sensation of an environmental or industrial toxin. If reliable methods of testing cutaneous sensation were available and found general acceptance, their use at different medical centers would allow comparison of sensation results not now possible.

Table 1.—Quantitative vs Clinical Touch-Pressure on Hand*

Quantitative Touch-Pressure Grade of Abnormality	Clinical Touch-Pressure Grade of Abnormality: Normal	Clinical Touch-Pressure Grade of Abnormality: Abnormal
Normal	22	0
Abnormal	19	15

*H_0 is rejected at the $P = .001$ level.

Table 2.—Quantitative vs Clinical Touch-Pressure on Foot*

Quantitative Touch-Pressure Grade of Abnormality	Clinical Touch-Pressure Grade of Abnormality: Normal	Clinical Touch-Pressure Grade of Abnormality: Abnormal
Normal	17	3
Abnormal	24	28

*H_0 is rejected at the $P = .001$ level.

MATERIALS AND METHODS

Cutaneous Sensation Laboratory

The laboratory was devised to make it convenient to test sensation on the dorsal surface of the hand or finger and on the dorsal surface of the foot or toe. The hand and foot had been chosen because they are distal limb sites that often have abnormalities of sensation in neurologic disease, because in health they are sensitive regions, and because the skin at these two sites is not usually callused. The finger or toe to be tested is cradled in modeling clay and the fingernail is affixed to the table top with masking tape to prevent excessive movement. A table was devised so that the top is isolated from any mechanical movement of the adjacent wall and floor. The table top is a 1-cm-thick slab of marble covered by wood and vinyl resting on rubber cushions which, in turn, rest on sand-filled upright compartments supporting the table top. The patient sits in a dental chair, which rests on a hydraulic platform that is mounted on a track for ease in positioning the patient in relation to the examining table.

Mayo Touch-Pressure System II

The Mayo Touch-Pressure System II has, in part, been described previously.[5] When an electrical pulse is supplied to the galvanometer motor with jewel bearings attached to the stimulating stylus, a small depression of the skin is produced. We discovered early that square-wave pulses could not be used. When higher amplitudes of stimulation are used, the stylus will bounce off the skin, resulting in a variable degree of impact that can not be quantified. To avoid impact, the mechanical wave form was shaped as described for our first-generation instrument.[1] The stylus rests on the skin with a static load of 100 mg. Accommodation of sensation to this static load occurs promptly. The stimulus is felt by the patient as a tapping or as light touch or as a buzz and is produced by a vertical downward displacement of the stimulating stylus.

The instrument has been designed to produce 31 levels of stimulation between 4.75 and 8.98 log (to base e) mg.[5] The increments in pressure of successive levels are based on a study of just noticeable differences (JND) of touch-pressure. From previous work, we found that just noticeable difference of touch-pressure sensation of finger could be described by the simple equation $\text{JND} = b + a\ (s)$, where $a = 0.1514$, $b = 0.1696$, and s = standard. The lowest level of stimulation was arbitrarily set at a value that was small enough so that it could not be felt by most children on their index finger. The number of levels of stimulation used (increments based on JND) was chosen so that the highest pressure values used would be recognized on all points, even on the toe of most healthy old people.

The stimulation sequence at a grid point is divided into six five-second intervals. The first five-second interval will be called the validation threshold (VT) sequence and the second through sixth intervals will be called rapid finding of threshold (RFT) sequence. In the five-second VT period, either a level 16 or a null stimulus is given. In the five five-second RFT sequences, stimulation is given initially at level 16 and at other levels, depending on the response, according to the algorithm shown in our previous publication.[5] If tapping is felt, it is signaled by a finger switch operated by the examiner. If the switch is not activated, a lack of feeling is assumed. The location of the grid point (column and row), stimulus given (either level 16 or null) during VT sequence, and the estimated threshold found in RFT in log (base e) mg are printed on paper tape.

After the completion of the VT and RFT sequence at the first grid point, the stimulating stylus is raised, traversed to the second grid point (in this study grid points are spaced 1 mm apart), and lowered to rest on the skin with a static load of 100 mg. The stimulation sequence at this and subsequent points (25 grid points) followed the sequence outlined above for the first grid point. Whether a level 16 or a null stimulus was given during VT sequence was predetermined at random for each point.

To score touch-pressure sensation at a site, the number of sensitive, insensitive, and too sensitive points were obtained. The mean estimated threshold in log (base e) mg, its standard deviation, and its coefficient of variation for sensitive points was estimated. Abnormality of touch-pressure sensation at a site was recognized either by an increase of insensitive points or by a raised threshold of sensitive points.

The results of the response to a level 16 or null stimulus at the 25 grid points was used as a rough test of whether the mean threshold obtained by the RFT sequence was approximately correct.

Evaluation of the validation sequence was done in two ways. First, we obtained a measure of reliability (P_1) among the n_1 points from the RFT sequence in which estimated threshold was greater than or equal to level 16. The second measure (P_2) was obtained from the remaining n_2 ($n_2 = 25 - n_1$) points for which estimated threshold was less than level 16. Let x_1 and

Table 3.—Quantitative vs Clinical Thermal Sensation in Hand

Quantitative Thermal Sensation	Clinical Thermal Sensation: Normal	Clinical Thermal Sensation: Abnormal
Normal	9	3
Abnormal	1	5

Table 4.—Quantitative vs Clinical Thermal Sensation on Foot

Quantitative Thermal Sensation	Clinical Thermal Sensation: Normal	Clinical Thermal Sensation: Abnormal
Normal	12	5
Abnormal	2	6

Table 5.—Quantitative vs Clinical Pain on Hand

Quantitative Pain Sensation	Clinical Pain Sensation: Normal	Clinical Pain Sensation: Abnormal
Normal	29	6
Abnormal	9	7

Table 6.—Quantitative vs Clinical Pain on Foot*

Quantitative Pain Sensation	Clinical Pain Sensation: Normal	Clinical Pain Sensation: Abnormal
Normal	39	21
Abnormal	3	9

*H_0 is rejected at the $P = .001$ level.

Table 7.—Density of Large Myelinated Fibers (MF) vs Touch-Pressure of the Toe

Patient	Age, yr	Clinical Touch-Pressure	Quantitative Touch-Pressure*	No. of Large MF/sq mm	Density of Large MF*†
2	43	A	A	1,232	A
4	58	N	A	2,426	N
6	29	A	N	3,058	N
11	63	A	A	311	A
15	66	A	A	483	A
19	49	A	A	415	A
21	55	N	A	2,869	N
22	52	A	A	109	A
24	56	...	N	4,303	N
28	26	A	N	2,380	N
38	49	A	A	247	A
40	57	N	N	2,661	N
41	38	A	A	289	A
45	74	N	A	1,264	A
48	67	A	A	157	A
50	69	...	A	1,067	A
51	52	A	A	48	A
59	55	N	A	260	A
61	61	N	N	2,830	N
63	16	A	A	55	A
64	55	N	N	2,641	N
66	47	N	A	2,542	N
71	54	N	A	738	A
76	47	N	N	2,299	N
77	48	N	A	3,125	N
93	54	A	A	2,737	N
100	66	N	N	1,887	A

*A indicates abnormal; N, normal.
†< 2,000 large MF/sq mm is considered abnormal.

x_2 represent the number of correct responses in the validation sequence among the above sets of sensitive and insensitive points, respectively. As a measure of reliability, using the n_1 sensitive points, we computed the probability (P_1) that in a sequence of n_1 independent trials the number of correct responses will be less than or equal to x_1, given that the probability of correct response on each trial is .75.

Small values of P_1 indicate that estimates of threshold at or above level 16 are not reliable. Similarly, to measure reliability among the insensitive points we computed P_2, the probability that in a sequence of n_2 trials the number of correct responses will be greater than or equal to x_2. Again, small values of P_2 indicate that estimates of threshold less than level 16 are not reliable.

Persons at various ages, without symptoms of disease of peripheral nerves or history of diseases predisposing to peripheral neuropathy, were used to provide reference values for the present study. Specifically, these subjects were used to estimate the 95% normal range.

Thermal Discrimination

To determine thermal discrimination on the blackened dorsal surface of the hand and foot, Minnesota Thermal Disks were used. Making use of the differences in heat transfer characteristics of copper (C), stainless steel (S), glass (G), and polyvinyl chloride (P), it was possible to estimate thermal discrimination using the pairs C and P, C and G, and C and S by the techniques described in our previous report.[2] In that study, we reported on the normative values on the forehead, and on the dorsal surface of hand and foot in 30 healthy persons of various ages. For analysis of thermal discrimination in this report, we summed the percentage of correct responses with the three pairs of stimulators and took the mean value.

Pain Sensation

Using the commercially available dolorimeter devised by Hardy and colleagues,[3] we estimated the pricking-pain sensation of the blackened skin of the dorsal surface of hand and foot in 69 healthy persons without known disease of the peripheral nervous system. The instrument was calibrated by methods described by Hardy et al. The results were corrected according to the formula provided by these authors for 33 C. To determine the threshold of pricking-pain sensation, we began at levels well below threshold and raised the intensity of the stimulus in increments of 5 mcal/sq cm/sec. We determined the 50% level at which stimuli were perceived as painful. In all cases, we provided stimuli that exceeded the threshold by at least 30 mcal/sq cm/sec to obtain a 100% painful response.

RESULTS

Quantitative measurement of cutaneous sensation was obtained on 107 patients with various kinds of neuromuscular disorders: chronic inflamma-

Table 8.—Summary Statistics

	N	Mean	SD
Clinical touch-pressure			
Normal	12	2,129	909
Abnormal	13	886	1,099
Quantitative touch-pressure*			
Normal	7	2,608	376
Abnormal	18	1,072	1,094

*Excludes patients 24 and 50.

Table 9.—Condition of the Clinical Touch-Pressure Sensation of the Toe and the Density of Large Myelinated Fibers (MF) of the Sural Nerve

Clinical Touch-Pressure Condition	Density of Large MF by Condition* Normal	Density of Large MF by Condition* Abnormal
Normal	8	4
Abnormal	3	10

*Normal indicates density $\geq$ 2,000 MF/sq mm; abnormal, density < 2,000 MF/sq mm.

Table 10.—Condition of the Quantitative Touch-Pressure Sensation of the Toe and the Density of Large Myelinated Fibers (MF) of the Sural Nerve

Quantitative Touch-Pressure Condition*	Density of Large MF by Condition* Normal	Density of Large MF by Condition* Abnormal
Normal	7	1
Abnormal	5	14

*Normal indicates density $\geq$ 2,000 MF/sq mm; abnormal, density < 2,000 MF/sq mm.

tory polyradiculoneuropathy, 17 patients; hereditary motor and sensory neuropathy or dominantly inherited hypertrophic neuropathy type of peroneal muscular atrophy, six; neuronal type of peroneal muscular atrophy, nine; hereditary motor neuropathy affecting distal muscles, seven; amyotrophic lateral sclerosis, six; spinocerebellar disease, four; muscular dystrophy, three; inherited neuropathies, 16; acquired neuropathies, 15; and unknown, 24. In many but not all patients, touch-pressure, thermal discrimination, and pricking-pain sensations were estimated by clinical and quantitative methods in both the foot and hand.

Using quantified stimuli, and considering the entire group of patients, an abnormality (95th percentile or greater) of touch-pressure sensation was found in 66.7% of feet and 55.4% of hands; of thermal discrimination in 27.8% of feet and 15.4% of hands; and of pricking-pain sensation in 18.2% of feet and 25.0% of hands. These results provide little meaningful information because a large variety of disorders of various severity are all lumped together. The figures, however, suggest that either an abnormality of touch-pressure sensation is more common or it is more readily recognized by the techniques used than are thermal discrimination and abnormality of pain sensation.

The results of the comparison of clinical vs quantitative touch-pressure sensation are shown in Tables 1 and 2. For the hand, the two methods produced the same conclusion (normal or abnormal) in 37 of 56 (66.1%) cases. In all 19 instances of disagreement, the quantitative measurement was abnormal and the clinical judgement was normal. In comparisons of this sort, it is desired to test the null hypothesis (H_0) that each method indicates abnormality with the same frequency. Under this hypothesis, one would expect differences to occur equally often in both directions. Clearly, this was not the case here in which all 19 differences were in the same direction, and H_0 is rejected at the $P < .001$ level of significance. For the foot, agreement occurred in 45 of 72 (62.5%) cases. In 24 of the 27 instances of disagreement the quantitative measurement was abnormal while the clinical judgement was normal. The hypothesis H_0 is again rejected, $P < .001$.

Comparisons of clinical vs quantitative assessment of thermal discrimination for hand and foot are shown in Tables 3 and 4, respectively. Agreement occurred in 14 of 18 (77.8%) cases in the hand, 18 of 25 (72%) in the foot. Although a diagnosis of abnormality was rendered more frequently by clinical judgement for both hand and foot, disagreement did not occur in enough cases to permit a test of H_0.

Comparison of clinical vs quantitative assessment of pain sensation is shown in Tables 5 and 6. Agreement occurred in 36 out of 51 (70.6%) cases for the hand and in 48 of 72 (66.7%) cases for the foot. Although abnormalities were detected in the hand more commonly with the quantitative method, the difference was not statistically significant. However, the greater frequency with which abnormalities were detected in the foot using clinical judgement was statistically significant, and in this instance H_0 may be rejected at the $P = .001$ level.

Morphometric data on sural nerve was available on 27 patients in this series. As a test of whether the clinical or quantitative assessment of touch-pressure would best correlate with loss of touch-pressure fibers in peripheral nerve, we compared these evaluations of touch-pressure sensation of the toe to morphometric data from 27 sural nerves from patients in this series. We used the number of large myelinated fibers (5.5μm and greater in diameter) per square millimeters of fascicular area as the histologic criterion that could be expected to correlate best with the state of touch-pressure sensation.

Actually, a direct comparison of low-threshold touch-pressure sensation to the density of large fibers assumes more information about the function of cutaneous nerve fibers than is now available, particularly about the nerves of man. Information about the function of Aα fibers of cutaneous nerves of man is incomplete.[4] Furthermore, it is not yet known with certainty that low-threshold touch-pressure receptors in acral parts of man are innervated only by Aα fibers. It may be that some Aδ fibers or some drC fibers also have such a function, although from our previous studies[6] of the nature of the sensation loss, of the type of abnormality of the compound action potential, and of morphometry of excised cutaneous nerves of man in various diseases, it seems most likely that low-threshold touch-pressure receptors are innervated by Aα fibers. An additional problem is that the density of large myelinated fibers is estimated within a nerve trunk, and may not reflect accurately the abnormality of the distal nerve fibers innervating cutaneous receptors. Finally, it is possible that a functional abnormality of the sensory apparatus may be present with or without a morphologic one.

Tables 7 and 8 show the touch-pressure and density data for 27 subjects, as well as summary statistics. It is apparent that the standard deviation of density of myelinated fibers in patients diagnosed as normal by quantitative measurement of touch-pressure is markedly less than that arising from clinical evaluation. Inspection of the data indicates the cause. Patients 59, 71, and 45 were classified as normal based on clinical evaluation; however, the density of large myelinated fibers in these subjects was found to be 260, 738, and 1,264 fibers per square millimeter, respectively, considerably less than what would be expected in healthy subjects. Table 9 shows the number of patients with clinically normal and abnormal touch-pressure sensation of the toe and whether the density of large fibers was normal or abnormal. Table 10 shows similar data for quantitative assessment of touch-pressure sensation abnormality to morphometric abnormality. Using the density of large fibers as a standard, a correct estimate of abnormal sensation by clinical examination was made in 72% of cases. In 12%, the clinical examination overestimated and in 16% it underestimated the fiber loss. Comparable figures for the quantitative examination were 78%, 18%, and 4%.

COMMENT

Quantitative measurement of cutaneous sensation, as described here, may be used as a quality control of the sensory examination done by the clinical neurologist. If it is to be used in this way, the instruments, the testing techniques, and the scoring techniques should be the best available. Although for each of the instruments we have utilized in this study the stimulus is constant, reproducible, and graded, the technique of testing and scoring is suboptimal for the touch-pressure instrument and the dolorimeter. For determination of touch-pressure sensation it would be preferable to use a two-alternative forced-choice (2AFC) technique. That this is the preferred technique of testing and scoring touch-pressure sensation has been demonstrated by Sekuler et al[7] using von Frey hairs—stimuli that are not accurately gradable or reproducible. In the tests of thermal discrimination we use a modification of the 2AFC technique. It is difficult to see how a technique of this type can be used to determine pain threshold. To illustrate using the radiant heat method, the identity of the null and test stimulus might be correctly identified by thermal rather than by pain sensation. In the Mayo Touch-Pressure System III, which is being developed at this time, a 2AFC technique is being used.

Probably the most important findings to come from this study is that there is a reasonably good correlation between the recognition of abnormality of cutaneous sensation by clinical methods and by quantitative methods, and between decrease of touch-pressure sensation and decrease in number of large myelinated fibers of cutaneous nerves. The study has shown further that clinical neurologists at our medical center tend to underestimate abnormalities of touch-pressure sensation.

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Brief Communications

Serum Dopamine-β-Hydroxylase Activity in Migraine

Fumio Gotoh, MD; Tadashi Kanda, MD; Fumihiko Sakai, MD; Masahiro Yamamoto, MD; Tsuneyuki Takeoka, MD

• Serum dopamine-β-hydroxylase (DBH) activity was measured during headache-free intervals in 17 patients with migraine and during the headache interval in 16 patients with muscle contraction headache, as well as in 40 normal subjects. The DBH activity was significantly higher in the migraine patients (46.5 ± 4.5 units) than in the controls (24.9 ± 2.4 units), whereas no significant difference was observed between the patients with muscle contraction headache (29.4 ± 4.5 units) and the controls.

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While it is assumed that patients with migraine exhibit hereditary vascular instability,[1] the pathophysiological mechanism of the complex cerebral vasomotor disturbance remains unsolved. Histochemical and ultrastructural studies have offered anatomical evidence for a rich sympathetic nerve supply to the cerebral vessels.[2] Thus, interest has again focused on the role of the autonomic nervous system in cerebral vasomotor control. Our recent data have demonstrated a loss of cerebral blood flow autoregulation in patients with severe impairment of the autonomic nervous system, such as Shy-Drager syndrome.[3] Increasing numbers of reports from other laboratories seem to agree on the importance of the autonomic nervous system in the regulation of cerebral vessels.

Dopamine-β-hydroxylase (DBH), the final enzyme in the biosynthesis of norepinephrine, is released via exocytosis in amounts proportional to the amount of released norepinephrine upon stimulation of sympathetic nerve endings.[4] Recent observations have revealed that DBH is highly localized in the blood vessels of various species, including human cerebral vessels.[5] The resting level of serum DBH activity varies widely in man and appears to be largely under genetic control.[6] Elevation of serum DBH activity after various kinds of stress and exercise suggests that acute changes in serum DBH activity may serve as an index of sympathetic activity.[7]

It is important to elucidate (1) if the sympathetic nervous system serves as a causative factor in the hereditary vascular instability of patients with migraine, and (2) if the sympathetic nervous system participates in the cerebral vasomotor disturbance occurring during an attack of migraine. As a preliminary step, serum DBH activity levels in patients with migraine were compared with those of patients with muscle contraction headache and with normal controls.

SUBJECTS AND METHODS

The Table shows the subjects studied. Classification of the headaches was based on the Ad Hoc Committee scheme.[8] Patients who received medication within two weeks of study were excluded. Cubital vein samples were obtained from patients during headache-free intervals and also during headaches. Patients rested for 30 minutes before blood sampling. The control group consisted of 40 apparently healthy adults of both sexes with the same age distribution as the headache patients.

Serum was stored at −20 C until analyzed. The DBH activity was determined, using the method of Nagatsu and Udenfriend.[9] Two aliquots of each sample were assayed and the mean value obtained was used for analysis. One unit of DBH activity represents the formation of 1μmol of octopamine per liter of serum after incubation for one minute at 37 C. All results were evaluated by Mann-Whitney's rank sum analysis.

Subjects Studied

	Men (Age Range, yr)	**Women (Age Range, yr)**	**Total (Age Range, yr)**
Classic migraine	2 (30-40)	4 (27-35)	**6 (27-40)**
Common migraine	1 (40)	10 (22-67)	**11 (22-67)**
Muscle contraction headache	7 (24-61)	9 (24-68)	**16 (24-68)**
Normal	25 (26-55)	15 (21-55)	**40 (21-55)**

RESULTS

Venipuncture had no effect on serum DBH activity in the five normal subjects tested. The distribution of serum DBH activity in 40 normal controls, 16 patients with muscle contraction headache (during the headache interval), and 17 patients with migraine (during the headache-free interval) are shown in the Figure. The serum values in normal controls exhibited a broad variation. They did not show an even distribution but showed a concentration toward lower values. The mean activity of the enzyme was 24.9 ± 2.4 units (mean ± SEM), and no differences were observed in DBH activity between male and female subjects. The mean activity in the group of muscle contraction headache patients (29.4 ± 4.5 units) was not significantly higher than that in the control group. On the other hand, the mean serum DBH activity in patients with

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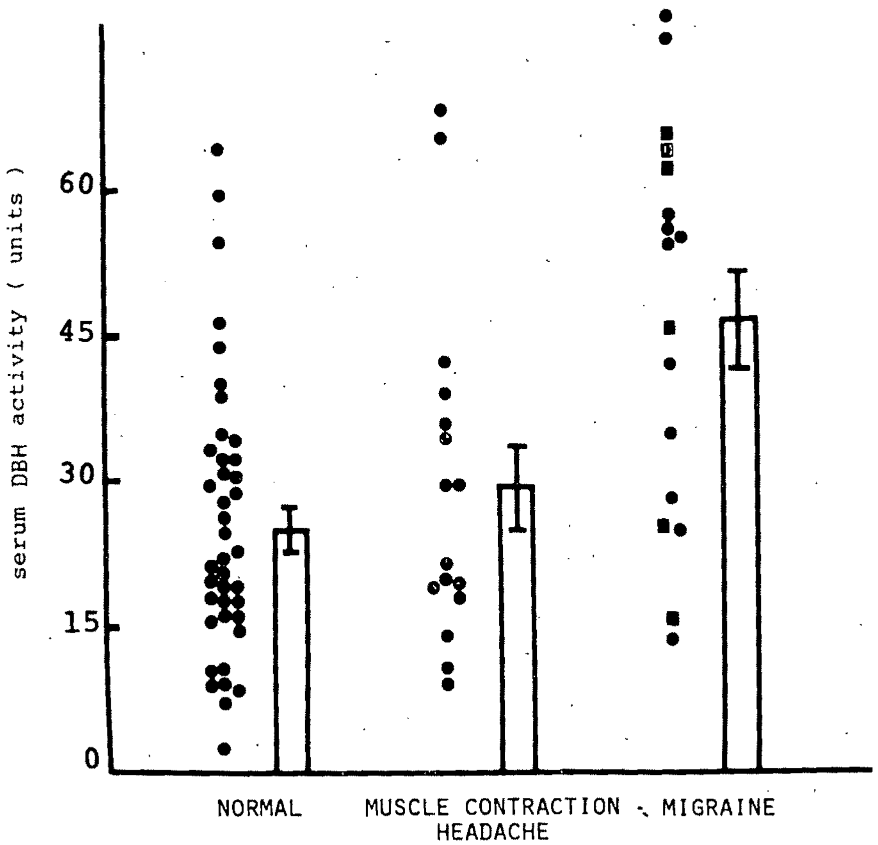

Distribution of serum dopamine-β-hydroxylase (DBH) activity in group of 40 normal controls, 16 patients with muscle contraction headache, and 17 patients with migraine. Squares indicate classic migraine and circles represent common migraine. Bar graphs represent mean ± standard error of mean for each group; $P < .01$ (normal vs migraine).

migraine (46.5 ± 4.5 units) was significantly higher ($P < .01$) than that in the control group. There were no significant differences in serum DBH activity between patients with classic and common migraine. The possibility of serum DBH activity being influenced by differing levels of circulating DBH inhibitors was ruled out by inhibition tests, using purified beef adrenal DBH.

COMMENT

If the sympathetic nervous system is involved in the pathogenesis of migraine, two possible mechanisms may operate: (1) abnormal sympathetic tone may be related to genetic predisposition in patients with migraine; and (2) excessive sympathetic nervous discharge may produce cerebral vasoconstriction in the period before headache.

The patients with migraine in this study had a high level of serum DBH activity during the headache-free interval, while the enzyme activity in serum from patients with muscle contraction headache studied during the headache interval was not different from that of the control group. The relevance of any apparent correlation between abnormal levels of serum DBH activity and particular dysfunctions of the sympathetic nervous system still remains controversial. Thus, a high serum DBH activity in patients with migraine might be related to some hereditary vascular instability of the brain and other organs. Knowledge of serum DBH activity levels in family members of patients with migraine may provide further biochemical data to enhance previous studies on the hereditary mechanism of migraine.

The second possibility mentioned previously suggests that the elevated serum DBH activity in patients with migraine may reflect a primary role for norepinephrine in the cerebral vasoconstriction occurring during an attack of migraine, and at least a part of the circulating DBH may be of cerebrovascular origin. This aspect of DBH's possible role in or relevance to migraine should be clarified when a substantial number of samples has been obtained both from the jugular vein and from arteries for evaluation at various stages of the migraine process.

The role of the sympathetic nervous system in the pathogenesis of migraine has long been a subject of considerable interest and discussion.[10] Although the physiological role and kinetics of serum DBH have not yet been satisfactorily explained and any interpretation of abnormal levels of serum DBH activity would at best be speculative, our present data provide some rationale on which to base subsequent studies of migraine.

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Evaluation of Patients With Progressive Intellectual Deterioration

Frank R. Freemon, MD

• Sixty consecutive patients with progressive intellectual deterioration were evaluated by a specific protocol. Eighteen (30%) were found to have an underlying disease potentially reversible by medical or surgical therapy. Sixteen patients had a specific diagnosable but untreatable disease as a cause of dementia. The laboratory and radiologic tests of the protocol that uncovered treatable illnesses were the radioisotope brain scan (two cases of bilateral subdural hematoma), the pneumoencephalogram (seven patients with normal-pressure hydrocephalus), thyroid function screen, and liver function studies (one case each). Unrewarding tests included serum barbiturate, bromide, vitamin B_{12}, and folate levels.

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Opinions differ concerning the best method to evaluate the adult patient with progressive intellectual deterioration, a symptom complex often referred to as dementia or chronic organic brain syndrome. While many experts recommend exhaustive medical, neurologic, and radiologic examination of each demented patient,[1-3] many practicing physicians consider dementia to be irreversible and undertake no evaluation at all. The present study attempts to determine the frequency and types of underlying medical illnesses and the most valuable laboratory and radiologic examinations.

SUBJECTS AND METHODS

Each patient admitted to the Nashville Veterans Administration Hospital between July 1, 1973, and June 30, 1975, for evaluation of a progressive decline in intellectual function over a period of months to years was evaluated by a specific protocol. The clinical history was obtained from relatives and other observers—not solely from the patient—with special attention to drug and alcohol use. Complete physical, neurologic, and mental status examinations were carried out. The following blood tests were performed: complete blood count, sequential multiple analysis, serum levels of barbiturates, bromides, vitamin B_{12}, and folic acid, serum VDRL, and serum fluorescent treponemal antibody (FTA). Chest and skull roentgenograms, an electroencephalogram, and a radioisotope brain scan were performed. Ophthalmologic consultants examined each patient under 40 years of age for Kayser-Fleischer rings. If the cause of dementia remained unknown, each patient whose health permitted surgery, in the event that normal-pressure hydrocephalus could be diagnosed, underwent pneumoencephalography. In each case, the cerebrospinal fluid (CSF) was examined using india ink, and was analyzed for cells, glucose, protein, and VDRL.

RESULTS

Sixty consecutive patients were evaluated (Table). All were men whose average age was 66.2 years.

Eighteen patients had an underlying treatable illness. Many patients had a depressed mood, but only in one did treatment with tricyclic antidepressants reverse the mental dullness and psychomotor retardation that had masqueraded as dementia. Seven patients had the clinical and pneumographic picture of normal-pressure hydrocephalus. Two patients, both chronic alcoholics, had bilateral subdural hematomas disclosed by radioisotope brain scan. One patient suffered from syphilis of the central nervous system (CNS) as demonstrated by positive CSF and serum VDRL and serum FTA, a history of primary syphilis, and typical physical findings including Argyll Robertson pupils. The initial liver enzyme analysis showed hepatic failure in one case. One patient had hypothyroidism. Five patients had mental changes associated with the abuse of multiple psychoactive drugs.

Although these 18 patients had treatable diseases, not all responded to treatment. All five patients with

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Summary of Dementia Evaluation at Nashville Veterans Administration Hospital Compared With Results From National Hospital, Queens Square, London

	Author's Data, No. (%)	**Marsden and Harrison,[6] No. (%)**
Treatable disease uncovered	18 (30)	19 (20)
Normal pressure hydrocephalus	7	5
Chronic drug toxicity	5	2
Resectable mass lesions	2	3
Depression	1	8
Other	3	1
Definable but untreatable disease uncovered	16 (27)	27 (29)
Multi-infarct dementia	5	8
Alcoholic dementia	4	6
Huntington chorea	4	3
Other	3	10
Unknown disease	26 (43)	48 (51)
Total	**60**	**94**

drug toxicity had complete reversal of the symptoms of intellectual decline that had prompted admission. Both patients with bilateral subdural hematomas had improvement, but not normalization, of intellectual function following surgical drainage through burr holes. Results with normal-pressure hydrocephalus were more disappointing. One patient died of a pulmonary embolus. One patient had substantial improvement and two had slight improvement with shunting. One was worsened and two others showed no change following the shunt. The patient with CNS syphilis showed no change in cerebral function after receiving high-dosage penicillin therapy. Treatment of the two patients with systemic medical disease produced unquestionable improvement.

Sixteen patients had a diagnosable, but untreatable disease. Seven patients had chronic alcoholism as diagnosed by specific criteria[4] associated with dementia, and mild to moderate cortical atrophy. Five patients had histories of multiple stroke-like episodes, and in these patients, the diagnosis of multi-infarct dementia was made.[5] These patients were not admitted for stroke care or cerebrovascular evaluation, but because of an apparent decline in intellectual function. All were hypertensive; autopsy in one showed lacunae throughout both frontal lobes. Four patients had choreiform movements and a history of dementia in a parent. The diagnosis of Huntington chorea was made in each of these subjects, none of whom were related. One patient had a glioblastoma. Two patients had static disease originally thought to be progressive, one with mental changes following severe head trauma and the other herpes simplex encephalitis. The remaining 26 patients had no specific diagnosis, despite undergoing the full protocol work-up.

Of the laboratory studies of the protocol, the brain scan was of value in identifying the subdural hematomas as well as the malignant tumor. Pneumoencephalography helped in the diagnosis of normal-pressure or occult hydrocephalus. The diagnosis of CNS syphilis was suspected prior to the return of the serum and CSF tests for syphilis. The diagnosis of hypothyroidism was a complete surprise; the patient had none of the classic clinical features of myxedema. The only hint of liver failure in the patient with hepatic dementia was the history of chronic alcoholism. Barbiturate level was positive in three of the five cases with drug-induced intellectual deterioration, but in all five cases, the extensive use of many drugs in high dosage was uncovered in the admission interview.

COMMENT

The Table compares the results of the present study with the only comparable published series, which is from National Hospital, Queens Square, London.[6] The London series originally included 106 cases, but 12 are excluded from the Table because psychological testing showed the patients were not actually demented. I included cases of depression and chronic drug intoxication in the Table, although the authors considered these patients to be suffering an intellectual decline that only simulated dementia. The lower treatable percentage and concomitant increase in cases of dementia of unknown cause in the London series probably represents a difference of initial selection. Our patients came from a variety of sources, some self- or family-referred, while the London series only included patients previously screened by a referring psychiatrist or neurologist.

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Cerebellar Degeneration With Hodgkin Disease

An Immunological Study

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• A 21-year-old woman with subacute cerebellar degeneration was found to have Hodgkin lymphoma. Radiation therapy for the lymphoma halted the progression of her neurological disease. Using an immunofluorescent technique, we found the patient's serum to have antibodies to cerebellar Purkinje cells.

(*Arch Neurol* 33:660-661, 1976)

To our knowledge, five cases of cerebellar degeneration with Hodgkin disease have been reported previously.[1-5] We describe a sixth case in a patient who has lived four years after the onset of her illness. Using indirect immunofluorescent staining, we sought evidence of an immunologic basis for her neurological disease.

REPORT OF A CASE

A 21-year-old housewife was well until April 1971, one month after the delivery of her second child, when she began to experience bilateral horizontal diplopia and mild occipital headache. A few weeks later she began to notice some "stiffness" in her legs and difficulty walking. In June she noticed slurring and slowness in her speech and clumsiness of her hands. She was hospitalized at that time, and was noted to have bilateral horizontal nystagmus on lateral gaze, a wide-based ataxic gait, dysarthria, and ataxia of her upper extremities. Lumbar puncture, electroencephalogram, posterior fossa and carotid angiography, brain scan, and ventriculogram were unremarkable. She was discharged with a diagnosis of probable multiple sclerosis.

The patient first sought our attention in October 1971, complaining of progressive deterioration of her gait, speech, and coordination. Her past history was unremarkable and there was no family history of neurologic or hematologic disease. The patient did not use tobacco or alcohol and had not been exposed to known toxins.

General physical examination was unremarkable except for mild obesity. There was no adenopathy or organomegaly. Neurological examination, including mental status, was unremarkable with the following exceptions: She had a wide-based ataxic gait and was unable to walk without two canes. There was mild ataxia on heel-to-shin and finger-to-nose testing, with the lower extremities more severely affected than the upper extremities. There was generalized weakness. Eye movements demonstrated bilateral coarse horizontal nystagmus without evidence of gaze paresis. The patient reported horizontal diplopia bilaterally.

Routine laboratory examination was unremarkable except for the demonstration of a mild iron deficiency anemia. Antinuclear antibody, lupus erythematosus preparations, and serum protein electrophoresis were within normal limits. A bone marrow examination was normal.

A routine chest roentgenogram showed a mass in the anterior mediastinum on the left side. The mass was biopsied, and proved to be a lymph node that was identified microscopically as nodular sclerosing Hodgkin disease. A spleen and liver scan, intravenous pyelogram, lymphangiogram, and exploratory laparotomy revealed no further disease involvement. Skull roentgenograms, EEG, and brain scan showed no abnormalities. Lumbar puncture revealed a normal pressure, with two mononuclear cells per cubic millimeter; protein level was 20 mg/100 ml; glucose level was 80 mg/100 ml. The cerebrospinal fluid electrophoresis was within normal limits. Roentgenograms from the first hospital were reviewed and found to be adequate and normal. A pneumoencephalogram showed no abnormality.

The patient's condition was diagnosed as stage I Hodgkin disease. The cerebellar symptoms were believed to be a remote effect of her Hodgkin disease and radiation therapy to the mediastinum was begun, with initial mild improvement. There was no further evolution or relapse of the neurological disease after completion of the radiation therapy and prednisone, 60 mg/day for three months. The patient has remained neurologically unchanged without further therapy for four years.

METHOD

Serum was collected from the patient prior to radiation or prednisone therapy and from appropriate controls. The sera were absorbed with human red blood cells to remove blood group reactive antibodies. Autopsy specimens of cerebellum were obtained from a histologically normal brain. Tissue blocks were quick frozen in dry ice and acetone, and were embedded. Sections 4μ in thickness were cut on a cryostat; they were air dried on microscope slides.

Unfixed tissue was used in all staining procedures. The indirect immunofluorescent staining technique was used. Tissue sections were overlaid with test serum and dilutions made in phosphate buffered saline for 30 minutes before washing in buffer and adding specific antibody conjugates. The conjugated antisera included antihuman IgG, IgA, IgM, anti-C3, antifi-

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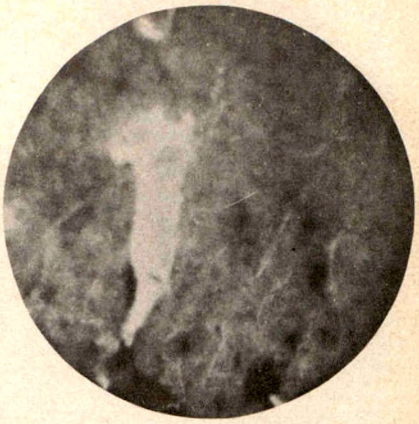
Indirect Immunofluorescent Cerebellum Staining by Serum From the Patient With Hodgkin Disease, Normal, and Neurological Control Patients

Patient	Disease	Cerebellum Staining
1	Hodgkin	No staining
2	Hodgkin	Trace Purkinje cell fluorescence
3	Normal	Trace Purkinje cell fluorescence
4	Normal	No staining
5	Multiple sclerosis	. . .
6	Multiple sclerosis	1+ Purkinje staining
7 (present case)	Hodgkin and cerebellar degeneration	3+ Purkinje-trace granular cell layer fluorescence
8	Amyotrophic lateral sclerosis	No staining



Fluorescence of Purkinje cell in cerebellar degeneration with Hodgkin disease (original magnification ×400).

brinogen and antialbumin. Some conjugates were prepared in the laboratory, while others were obtained commercially. All were absorbed extensively with tissue powder to reduce nonspecific staining. Stained sections were mounted in pH 7.6 buffered glycerol and examined under a fluorescent microscope using incident light.

RESULTS

The results of indirect fluorescent staining are shown in the Table. A moderate degree of background and autofluorescence was seen in seven of the eight patients. It was common to see quite bright reddish autofluorescence around the cerebral cortex specimens. It was common to find sera causing weak fluorescence of neurons. The serum from our patient caused strong fluorescence of Purkinje cells and weak staining of the granular layer of the cerebellum (Figure). The reaction was seen mainly with anti-IgG conjugates, and this reaction could be quenched considerably by absorption of this antiserum with IgG, but not with other serum proteins. Staining using other conjugates, including anti-C3, was relatively weak. The granular layer fluorescence seemed less specific and could not easily be absorbed out even when the anti-IgG serum was treated with IgG.

The staining of the Purkinje cells seemed to be cytoplasmic, but was possibly membrane and nuclear as well. The antigens involved are not known. In spite of strong fluorescence seen at lower dilutions of the patient's serum, the effect was not present above a 1:20 dilution. The reason for this rapid drop off of activity is not clear.

COMMENT

Brain and colleagues[6] pointed out the relation between subacute cerebellar degeneration and carcinoma. A more recent review has been prepared.[5] The most common sites of neoplasm are the lung and ovary, followed by lymphoma and Hodgkin disease.[4] Our patient is the fifth to our knowledge to have cerebellar degeneration with Hodgkin disease. The occurrence of ataxic gait, ataxia of upper extremities, dysarthria, diplopia, and nystagmus is characteristic. The vertigo seen in other cases was absent in our patient.

The cause of this syndrome is unknown. The possibility of viral or autoimmune disease is frequently mentioned. The presence of antibrain antibodies has been noted in sensory carcinomatous neuropathy both by complement fixation[7,8] and immunofluorescent[9] methods. Ours is the first report to our knowledge of antibodies against Purkinje cells in subacute cerebellar degeneration complicating neoplasms.

It is impossible to state whether or not these antibodies in the patient's serum were contributing to her neurological problem or were just there as a secondary phenomenon. Central nervous system tissue can give problem background staining in the immunofluorescent technique, yet other patient sera examined did not give the pattern observed with the present case. It would seem worthwhile to extend these staining procedures to other similar problems where a direct immunologic tissue damage effect seems possible.

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Letters and Clinical Notes

Brain Specialization for Language: Not Dependent on Literacy

To the Editor.—It may be that brain specialization for language does not depend on literacy as Damásio and co-workers contend (*Arch Neurol* 33:300, 1976), but we do not believe it has been proved in their study any more than the converse was proved by ours.[1] They note that, of their 38 illiterate patients, 24 had focal lesions of the left hemisphere and 14 of the right. Twenty of the 24 were aphasic. These numbers raise the suspicion that the illiterate patients may have been preselected, possibly by avenue of referral for left hemisphere lesions and, conceivably, aphasia. Also, one cannot tell from their study how many of the 209 literate patients had left or right hemispheric lesions; therefore, the comparison of literate and illiterate patients for aphasia is not possible.

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1. Cameron RF, Currier RD, Haerer AF: Aphasia and literacy. *Br J Disord Commun* 6:161-163, 1971.

In Reply.—Drs Currier, Haerer, and Farmer raise the suspicion that illiterate patients may have been preselected for aphasia or left hemisphere lesions by avenue of referral. This may be true, but, if so, literate patients have also been affected by the same factor, and, since we are making between-group comparisons, the argument is not valid.

In reply to the question about left vs right hemisphere lesions in literate patients, we have evaluated another group of 225 right-handed focal brain-damaged patients studied in the same facility and selected in the same manner. The results are summarized in the Table. The distribution of left and right hemisphere lesions did not differ for the two groups ($\chi^2 = 1.403$; $df = 1$; NS). Furthermore, the frequency of aphasia among patients with focal lesions in the left hemisphere did not differ for the literate and illiterate groups ($\chi^2 = 1.403$; $df = 1$; NS). Similarly, irrespective of the side of lesion, the proportion of literate and illiterate brain damaged patients with aphasia (63% vs 67%) was indistinguishable ($Z = .523$; NS).

Also, Drs Currier, Haerer, and Farmer compared the results of the paper by Cameron and co-workers (*Br J Disord Commun* 6:161, 1971) with our own, saying that our work does not prove the contention anymore than theirs demonstrated the contrary. However, the fact that (1) illiterates *do* become aphasic, and (2) when they do, their aphasic pictures are structurally *indistinguishable* from the aphasias of literate people, effectively proves that brain specialization for language in such patients cannot have depended on literacy, since there had been none. Indeed, such a conclusion might even have been drawn from the study of Cameron et al, in which at least one third of the illiterate patients developed aphasias, not to mention their group of so-called semiliterate, in which another two thirds became aphasic. In their study, too, brain specialization for language had to be, of necessity, a "preliteracy" gift.

We are prepared to believe, like Cameron and associates, that *some* illiterates do not become aphasic, but we would like to see evidence of damage to the aphasia-producing areas of the left hemisphere in every case where aphasia failed to appear. We are also prepared to accept that illiterate aphasics perform at a lower level in linguistically demanding tasks and that their recovery from aphasia is quicker and better. However, this does not imply that literacy is a prerequisite for language-specialized brain structure.

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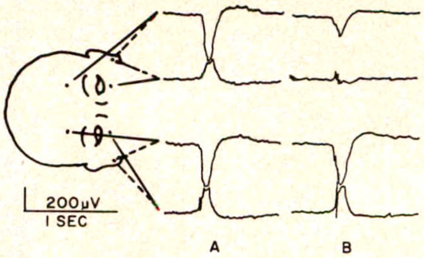
Evaluation of 225 Right-Handed Focal Brain-Damaged Patients

	No. (%) of Patients With		
	Left Hemisphere Lesions		
	Aphasic	Nonaphasic	Right Hemisphere Lesions
Literate (n = 182)	115 (63)	42 (23)	25 (14)
Illiterate (n = 43)	29 (67)	5 (12)	9 (21)

Absence of Bell Phenomenon During a Blink

To the Editor.—A recent article by Jacobs and Bender (*Arch Neurol* 33:289, 1976) warrants clarification of Bell phenomenon. Bell implied that an upward rotation of the eyes took place during any brief eye closure.[1] However, Hall[2] questioned the presence of Bell phenomenon during a spontaneous blink because of its short duration. A few attempts to estimate an upward ocular rotation during a blink yielded a figure of a few degrees at most.[3,4]



Electro-oculogram of a blink by a normal individual when eyes are in primary position, with both eyes open (A) and after the left eye is closed (B). (Electroencephalograph with the time constant 0.12 seconds.)

The typical appearance of electro-oculogram (EOG) of a blink is familiar to electroencephalographers (Figure, A). The EOG of a blink occurring after an eye is closed is shown in B of the Figure. There is an obvious potential difference between two sides, which makes doubtful the presence of an upward ocular rotation during a blink. A symmetrical potential change is expected during vertical ocular rotation in a normal individual, and there is no reason to believe the ocular rotation is asymmetrical during this maneuver. Barry and Jones[5] demonstrated the generation of electrical potential by a moving eyelid. The mere movement of the upper eyelid was enough to produce the potential change equivalent to that during a blink.[6] Therefore, caution is needed to estimate vertical ocular rotation from EOG. Jacobs and Bender attempted to correlate corneal movements under the closed eyelids, therefore ocular rotation, to EOG. However, rapid movement of the eyelid makes such observation impossible during a blink.

Additional support comes from observations of the absence of Bell phenomenon in subjects with unilateral peripheral facial paralysis during spontaneous blinks that take place in the nonparalyzed side. Bell phenomenon occurs as soon as these subjects are asked to close their eyes. Thus, it appears that the cerebral cortex participates in the neural mechanisms involved in Bell phenomenon, and it does not occur with every eye closure.

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In Reply.—Our article does not deal with the question of whether or not Bell phenomenon occurs during spontaneous blinks of short duration. We made no attempt to analyze oculomotor activity during blinking.

We studied the effects of eyelid closure on oculomotor function in patients with palatal myoclonus. Vertical ocular motions synchronous with the beat of the palatal myoclonus occurred only during "volitional" prolonged eyelid closure or attempted closure against resistance. These eye motions were a specific effect of active continuous eyelid closure and could not be obtained by sensory-induced reflex eyelid closure.

The ocular excursions were recorded by DC electro-oculogram. Both voluntary blinking and eyelid fluttering while the lids are closed have a typical appearance on the DC EOG. Neither blinking nor eyelid fluttering interferes with accurate recordings of the position and movements of the globes beneath the closed lids by DC EOG. The angular motion of the eye can be accurately determined from the EOG pen deflection when careful repeated calibrations are performed. Such quantitative recordings have been successfully obtained during prolonged periods of wakefulness and full nights of sleep, and are reported in detail elsewhere.[1]

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Giant Cell Tumor of the Temporal Bone

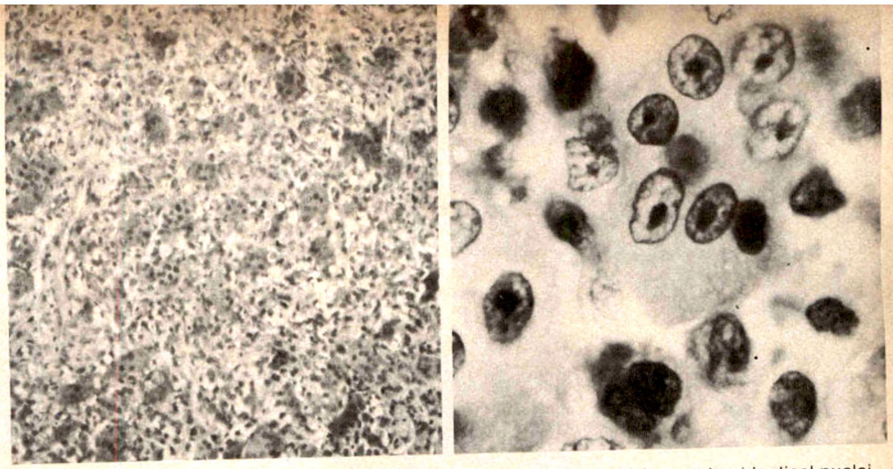
A patient with giant cell tumor of the temporal bone was treated with radiation therapy. Although the symptoms were relieved temporarily, inoperable tumor growth developed.

Report of a Case.—We examined a 61-year-old man who had developed vertigo three months prior to hospital admission and two weeks later, diminished hearing and tinnitus in the right ear. One month prior to admission, he became hoarse and developed a dysphagia.

Physical examination showed a postauricular bruit bilaterally. There was a mild right facial palsy as well as diminished hearing in the right ear. He was hoarse, had difficulty swallowing, and his tongue deviated to the right. The cerebrospinal fluid had a protein content of 81 mg/100 ml.

A red mass was seen behind the right tympanic membrane. X-ray films showed an erosive or destructive lesion involving the right petrous bone, jugular fossa, occipital bone, and occipital condyle.

A biopsy specimen of the lesion taken through the right ear showed "benign giant cell tumor" (Figure) Radiotherapy employing Cobalt 60 radiation therapy slightly improved the patient's symptoms, but one year later there was radiologic evidence of inoperable tumor growth.



Left, Low-power view of tumor, showing numerous giant cells with multiple, regular, identical nuclei. Right, High-power view. Stroma shows increased cellularity, but individual cells are uniform.

Comment.—Along with glomus jugulare tumor, differential diagnosis in this patient included cholesteatoma, metastasis, reticuloendotheliosis, reticulum cell sarcoma, fibrosarcoma, osteosarcoma, plasmacytoma, secondary metastatic lesions, or a "brown tumor" of hyperparathyroidism. Clinically, a brown tumor can be ruled out in the present case because levels of serum calcium and phosphorous were normal.

There has been one report of cure with radiation therapy of a giant cell tumor of sphenoid bone,[1] but no cures of temporal bone lesions have been reported. In hindsight, surgical treatment might have been preferred in this case.

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Unilateral Proptosis and Visual Field Defect Associated With Hydrocephalus

Patients with hydrocephalus may have ophthalmologic signs, including visual field defects. Proptosis has been reported rarely to result from hydrocephalus. The subject of the following clinical note had unilateral proptosis and visual field defects associated with aqueductal stenosis.

Report of a Case.—Four years prior to admission, this 46-year-old woman sustained blunt trauma to the forehead. Subsequently, she lost vision in the right eye. Several months prior to admission, bifrontal headaches and urinary incontinence occurred. Proptosis and chemosis of the right eye developed over five days, prompting admission to the hospital. There were no symptoms of endocrine dysfunction.

Pertinent findings on physical examination included dementia, severe proptosis, chemosis, ophthalmoplegia, and amaurosis of the right eye. Vision in the left eye was 20/100, with a superior temporal quadrantanopsia. Funduscopic examination of the right eye showed optic atrophy, with sharp disk margins and no venous engorgement. The left fundus was normal.

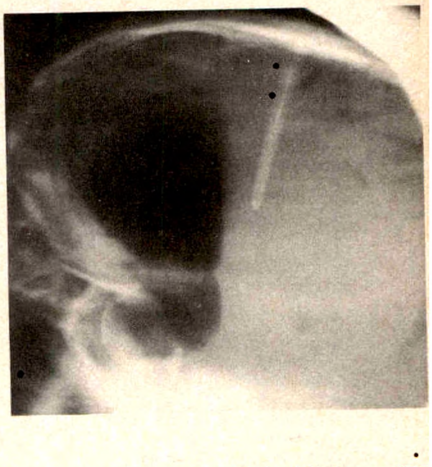
Skull x-ray films showed a massively enlarged sella. Orbital x-ray films showed intact orbital plates and normal optic canals. Carotid angiography showed only ventriculomegaly. Ventriculography combined with pneumoencephalography demonstrated aqueductal stenosis and enlarged lateral ventricles. The dilated third ventricle filled the sella turcica (Figure). Findings from endocrine studies were normal.

Although the relationship between the hydrocephalus and protosis was not clear, a ventriculoperitoneal shunt was inserted to control the hydrocephalus. Three days later, the chemosis began to resolve. On the sixth postoperative day, the shunt malfunctioned. Concurrent with this, chemosis and ophthalmoplegia returned. Within several days, the shunt began to function spontaneously. The chemosis, proptosis, and ophthalmoplegia disappeared, as did the quadrantic field defect. Urinary incontinence improved, as did the patient's dementia.

Comment.—Previous authors have reported visual field defects, including quadrantic defects in patients with ventricular enlargement.[1,2] These findings have been attributed to pressure exerted on the optic chiasm by the dilated third ventricle. In the same manner, the dilated third ventricle in our patient may have acted as an intrasellar mass, causing secondary visual field compromise.

Several authors have reported exophthalmos associated with hydrocephalus. In one report, the exophthalmos was unilateral and associated with an ipsilateral orbital plate defect.[3] The other report details bilateral proptosis in a patient with associated thyroid dysfunction.[4]

Blow-up film from air ventriculogram showing ventriculomegaly and intrasellar positioning of the third ventricle.



In an extensive review of patients with unilateral exophthalmos, Van Buren et al[5] refer to a group of patients whose proptosis resulted from venous hypertension. They note that asymmetric compression of the orbital venous drainage through the cavernous sinus should be a rare mechanism in view of the relatively free collateralization in this region. However, there are individual cases in which this mechanism has been well documented, especially in sellar and parasellar lesions.

In our patient, the third ventricle may have acted as an intrasellar mass, causing both optic chiasm and cavernous sinus compression. The dramatic response of this patient's signs to cerebrospinal fluid diversion and their return with shunt malfunction suggest that the findings of unilateral proptosis, visual field defect, and hydrocephalus are interrelated.

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Birth Order and Left-Handedness

Bakan[1] proposed the hypothesis that left-handedness is associated with "stressful prenatal and birth conditions." He equated first and fourth or higher birth order with greater stress than second and third birth order. In male university students, he found that first or fourth and higher birth order was acknowledged more commonly by left-handers than by right-handers. In females, however, the differences in birth order between left- and right-handers were smaller. However, Hubbard,[2] in his study of university students of both sexes, found that right-handers rather than left-handers had the higher frequency of first or fourth and higher birth order.

To resolve this discrepancy, 488 sixth-grade students and their 104 fifth-grade-age peers, who would have been in the sixth grade had they not repeated a grade, were questioned about birth order ("How many older brothers and sisters do you have?") and about five measures of handedness ("With which hand do you write . . . hammer . . . use a toothbrush . . . throw a ball . . . cut with scissors?"). Our findings for the writing task are presented in the Table. Similar results were obtained for the other four tasks.

We confirmed Bakan's finding that the strongest birth order effect is in males. Hubbard did not examine the relationship between birth order and handedness in each sex separately. This may, in part, account for his failure to demonstrate a significant relationship between handedness and birth order.

Risk/100 Children in Each Birth Order Category of Preferring the Left Hand for Writing

	Birth Order			
	1	**2,3**	**4,5**	**6+**
Girls	8.7	10.2	9.5	17.9
Boys	10.9	5.0	13.6	18.5

The use of four birth order groupings provides us with three findings not available previously. First, the risk of left handedness is relatively high in *both* first and fourth and higher birth order boys. Second, the risk of left-handedness tends to be highest in the highest birth orders. This "dose-response" relationship is additional support for Bakan's hypothesis.[3(pp21,235-237)] Third, the risk of left handedness in boys as a function of birth order has a U-shaped distribution. Fetal deaths[3(pp324,325)] and congenital anomalies of the neural tube[4] also have U-shaped distributions of risk as a function of birth order. This suggests that the relationship between birth order and handedness is a complex one and may reflect environmental factors operating at any of several points in time during pregnancy.

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Sensory Losses in Poliomyelitis

Sensory losses in poliomyelitis are rare,[1-3] but we recently cared for such a patient with both paraplegia and severe sensory disturbances.

Report of a Case.—A 19-year-old soldier had noted back pain, neck stiffness, headache, muscle aches, and temperatures of 38 C for eight days. At age 1 year, he had received the formaldehyde-inactivated polio vaccine (Salk). At 4 years of age, he had had tuberculosis of the lumbar spine and had received adequate treatment.

On admission, his temperature was 38 C and there was mild nuchal rigidity. The remainder of the examination was normal. Routine laboratory values were normal; lumbar puncture showed normal opening pressure with clear fluid containing 500 cells per cubic millimeter, 85% of which were polymorphonuclear leukocytes. The protein concentration was 60 mg/100 ml; glucose level, 60 mg/100 ml; smears for bacteria and acid-fast bacilli, negative; and cultures, sterile. Treatment with intravenously administered ampicillin, 12 gm/day, commenced.

Twenty-four hours later, urinary retention developed, accompanied by flaccid paralysis of the lower extremities. An L-1 motor level of paraplegia developed, with mild weakness of the upper extremities (grade 4/5 muscle strength). Sensory losses included hypesthesia to L-3 level, with position and vibration senses lost in the left leg.

Lumbar spine films showed slight scoliosis; myelography results were normal. Type 1 virulent poliovirus was isolated from the feces but not from the cerebrospinal fluid (CSF). Serum neutralizing antibodies titer against type 1 poliovirus were 1:256, and against both types 2 and 3 were 1:4. Repeated examinations of all antibody titers two months later showed no increases.

Antibiotic therapy was discontinued. Sphincter control slowly returned. The hypesthesia improved slightly, followed by a mild increase in strength in the upper extremities. Presently, the patient walks with crutches and leg braces, but L-3 hypesthesia remains unchanged.

Comment.—The clinical presentation of this case was consistent with the diagnosis of poliomyelitis except for the sensory disturbances, which simulated transverse myelitis and led to performance of unnecessary myelography. The CSF chemical analysis and the negative stains and cultures excluded the possibility of tuberculous meningitis secondary to reactivation of the vertebral tuberculosis. The fecal isolation of type 1 virus together with the elevation of antibody titer confirmed poliomyelitis infection.

The unusual features of the patient's disease were the marked sensory disturbances. Such a presentation of spinal poliomyelitis may mimic transverse myelitis and lead to unnecessary diagnostic procedures and treatments,[1,2] as occurred in this patient.

The posterior root ganglia of the spinal cord are frequently involved in poliomyelitis, and lesions have also been found in the white matter of the lateral and posterior columns of the spinal cord. These changes may explain sensory disturbances.

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Books

Atlas of Gross Neurosurgical Pathology, by Klaus J. Zülch, 228 pp, 379 illus, approx $50, Springer-Verlag, 1975.

In his *Atlas of Gross Neurosurgical Pathology*, Professor Zülch has presented 379 beautiful illustrations, most (317) of brain tumors and a few of inflammatory, hemorrhagic, necrotic, and hydrocephalic disorders. These gross illustrations are complementary to his *Atlas of the Histology of Brain Tumors* (Springer-Verlag, 1971) and to the *Handbuch der Neurochirurgie*, volumes 1 and 3 (Springer-Verlag, 1956 and 1959). As such they are "intended to give the practicing neurosurgeon, neuroradiologist, neuropathologist and neurologist the concise information they need for diagnostic purposes concerning the aspect, site, and malignancy of tumors and other space-occupying lesions in the brain." In keeping with the format of an atlas, the text is short and the bibliographic citations limited.

How well does Professor Zülch succeed? Without exception the illustrations are superb, the specimens clearly dissected and sharply focused, and at first glance one would have to admire their presentation in this convenient format, which will be useful to anyone desirous of seeing gross neuropathologic lesions, especially of brain tumors. Since practically all have been obtained at autopsy, one must recognize that, as such, they are almost all fatal, end-stage examples. Indeed, by my count 154 of 186 qualifying adjectives in the figure legends vary from "large" (56) or "marked" (25), to "extensive" (20), "huge" (15), "enormous" (14), "massive" (21), "giant" (five), and even "grotesque" (one). Only 25 adjectives are of the opposite extreme: "small" (15), "little" (92), "minimal" (one), and "incidental" (two). To these adjectives one can add 37 cuisinary terms, ranging from "pea" (five) and "bean" (four), through "cherry" (six), "walnut" (five), "apple" (four), to "tangerine" (two), and even "mandarin" (one). But, except for students and residents preparing for examinations, who really needs so many illustrations of such lesions? Almost certainly not "the practicing neurosurgeon, neuroradiologist, neuropathologist and neurologist" to whom the work is directed, since they are or should be primarily interested in the earlier stages of these diseases, when the tumors are smaller, less hemorrhagic, less necrotic, surrounded by less edema, and producing much less distortion and herniations of brain tissues through the tentorial notch or foramen magnum.

Furthermore, there must be a limit to the gross varieties of brain tumors. The late Keith Bradford, Professor of Neurosurgery of Baylor University Medical College, once confided to me that there were only two kinds of tumors: hard and soft, ie, those that can be aspirated through a sucker and those that cannot. One could expand this by admitting that tumors may be intraventricular, parenchymatous, or extracerebral, and that they may be variably solid or cystic; variably hemorrhagic and necrotic or only slightly discolored; variably sharply or poorly circumscribed; or variably spherical, hemispherical, or otherwise shaped. The combinations and permutations may seem large, but in practice the variations are surprisingly few.

In the short text accompanying an atlas an author can hardly be anything but dogmatic. The discussion on prognosis seems remarkably redundant, however, attempting to harmonize various histologic classifications as "grades I, II, III, and IV" and "benign, semibenign, semimalignant and malignant" become more or less synonymous with "isomorphous" or "polymorphous" (with a few examples of "anisomorphous," "amitotic/oligomitotic," or "polymitotic" added occasionally). The redundancy becomes more apparent when Professor Zülch states that ependymomas of the ventricles are associated with "cure or survival of 5 and more years." Most authors would agree that they certainly appear to be benign, both grossly and microscopically, and should be curable by excision alone, but we could find only a single example of five-year survival after surgery alone in 43 intraventricular ependymomas followed up in two cities (*Arch Neurol* 32:731-739, 1975). Admittedly, our study was published too late to be considered in this *Atlas*, but one can only wonder at the accuracy of comparable statements on page 51: "Another characteristic of the ependymoma of the cerebral hemisphere is a tendency to recur even after 'total' removal. The other ependymomas, fortunately, do not share these traits." And there follow ten examples of intraventricular ependymomas, obviously fatal, probably operated on and recurrent, but not specifically recorded as nonrecurrent. At least, one should be suspicious that these ten cases do not substantiate Professor Zülch's clinicopathologic correlations quoted above.

These gross photographs are excellent, so far as they go, but the text could be shorter, even completely eliminated, as a first step toward defining the real biology of brain tumors. Such definitions are much more complicated than gross photographs, arguments about histologic gradings, histogenesis, sex ratios, age ranges, and sites of preference. The clinical follow-ups become important, and Professor Zülch's 9,000 cases could provide the basis for these important definitions.

Ellsworth C. Alvord, Jr, MD
Seattle

Basic Mechanisms of Ocular Motility and Their Clinical Implications, edited by G. Lennerstrand and P. Bach-y-Rita, 584 pp, $60, Pergamon Press Ltd, 1975.

An international symposium emphasizing the clinical implications of basic ocular motor mechanisms was held in June of 1974 at the Wenner-Gren Center in Stockholm. The resultant text contains the scientific papers and clinical discussions presented, and preserves the symposium's stress on the symbiosis of basic and clinical research. It is divided into three main sections: peripheral mechanisms, central mechanisms, and free papers.

The first section, on peripheral mechanisms, contains excellent papers on the structure and function of cells, muscle fibers, and motor units, in addition to studies of extraocular muscle forces in normal and abnormal ocular motor systems. In the central mechanisms section, the topics presented include the vestibulo-ocular reflex, plasticity, cerebellar influences, ocular motor control, and effects on vision. Both sections contain clinical discussions that relate the findings of the basic research to clinical observations. The contributions in the final section, free papers, cover a very wide range of topics related to ocular motility. Their variety and quality complement those of the first two sections, and make this volume a "state-of-the-art" collection of basic and clinical research in ocular motility.

In addition to erasing the arbitrary clinical/nonclinical division of ocular motor research, this text, by the varied nature of the contributors' backgrounds, makes an important statement about the benefits of interdisciplinary approaches to research. It is a source book for neuro-ophthalmologists, bioengineers, and ocular motor and visual physiologists, and belongs on the shelves of all medical school libraries as well as neurology and ophthalmology departmental libraries.

Louis F. Dell'Osso, PhD
Miami, Fla

American Neurological Association, 1875-1975: Centennial Anniversary Volume, edited by Derek Denny-Brown, Augustus S. Rose, and Adolph L. Sahs, 622 pp, $25, New York, Springer Publishing Co, 1975.

The American Neurological Association celebrated its 100th anniversary in June 1975, and in honor of the occasion brought out this handsome volume. The editors put considerable effort into looking at both recent and remote history of neurology in the United States, and spared no effort compiling anecdotes and other minor information that convey a sense of humanity to the individual biographies.

The book gives a history of neurology from many standpoints. General overviews include an introduction by Houston Merritt and historical excerpts from J. R. Hunt and C. K. Mills from the semicentennial volume in 1924. Biographies of ANA presidents follow, and the book then describes a regional history of neurology in North America. Governmental organizations devoted to supporting and furthering the conquest of neurological diseases are discussed, as are the contributions of neurology to the military services. Finally, a useful appendix lists training centers and present and former members of the American Neurological Association. Doctors Denny-Brown, Rose, and Sahs have made an exceptionally effective contribution to the lore of American neurology, and anyone interested in its history will want this book.

Fred Plum, MD
New York

Malnutrition and Brain Development, by Myron Winick, 169 pp, $9.95, Oxford University Press, 1976.

Nutrition and the Developing Nervous System, by Philip R. Dodge, Arthur L. Prensky, and Ralph D. Feigin, 538 pp, $49.50, CV Mosby Co, 1975.

Normal and Abnormal Development of the Human Nervous System, by Ronald J. Lemire, John D. Loeser, Richard W. Leech, et al, 421 pp, $27.50, Harper & Row Publishers, 1975.

These three valuable books, each in its own way, emphasize the recent rapid growth of knowledge concerning man's early neurological development. They differ substantially in content and style and direct themselves towards somewhat different audiences, but all deserve attention.

Winick's monograph, the shortest of the three, achieves the considerable feat of being sufficiently narrative to be read in one sitting, yet detailed enough to provide an excellent summary of its topic. His research has contributed much to his theme, giving him a surefooted capacity to say as much as necessary and no more about the neurochemical development of brain and how it depends on exogenous nutrients. His evidence is strong that in animals either uterine or early postnatal nutritional deprivation can produce permanent stunting of brain and body size, as well as adverse behavioral effects. He thinks that the same holds true for man, and logic would demand such a view, but admits that the human parallel can't be proved yet, largely because social and nutritional factors have been impossible to separate in most blighted populations. Read it, you'll enjoy it.

The volume by Dodge, Prensky, and Feigin provides an encyclopedic resource of the first order. Much more a reference source than a personal point of view, the book is an excellent summary of what is known about normal biochemical, physiologic, and psychologic development of the brain, then relates these functions to normal and abnormal nutrition. Included in their comprehensive coverage are the effects on the developing brain of minerals and vitamins as well as thyroid deprivation and enzyme-dependent inherited aminoacidurias. The discussions are long, fact-filled, and balanced. Abundant referencing accompanies each section. It gives a reviewer great satisfaction to examine a book that is not only first in its field, but so well done that it probably will withstand challenge sufficiently well to become a classic. *Nutrition and the Developing Nervous System* risks having such success.

The book by Lemire, and colleagues combines some of the best features of both the above volumes. One of the authors, Ellsworth C. Alvord, Jr, has given 30 years of illuminating study to the developmental malformations of the nervous system, and his collaborators have shared and extended his insights in recent years. What results is an authoratative text on morphological central nervous system development, normal and abnormal, presented in declarative style, full of original data, diagrams, and tables, yet comprehensively incorporating and referencing the studies of others. What a pleasure it is to read a book that has a point of view and doesn't waffle on every item with endless "on the one hand, on the other." Much of what the book contains has been said before, but seldom so clearly. What hasn't been done before is to effectively arrange embryology and postnatal neurological development as a continuum, showing that the line sometimes leads all the way into adult life before producing neurological problems that require clinical attention. Few clinical neurobiologists, whether working with adults or children, can fail to learn from these pages, and many will find them indispensable.

Fred Plum MD
New York

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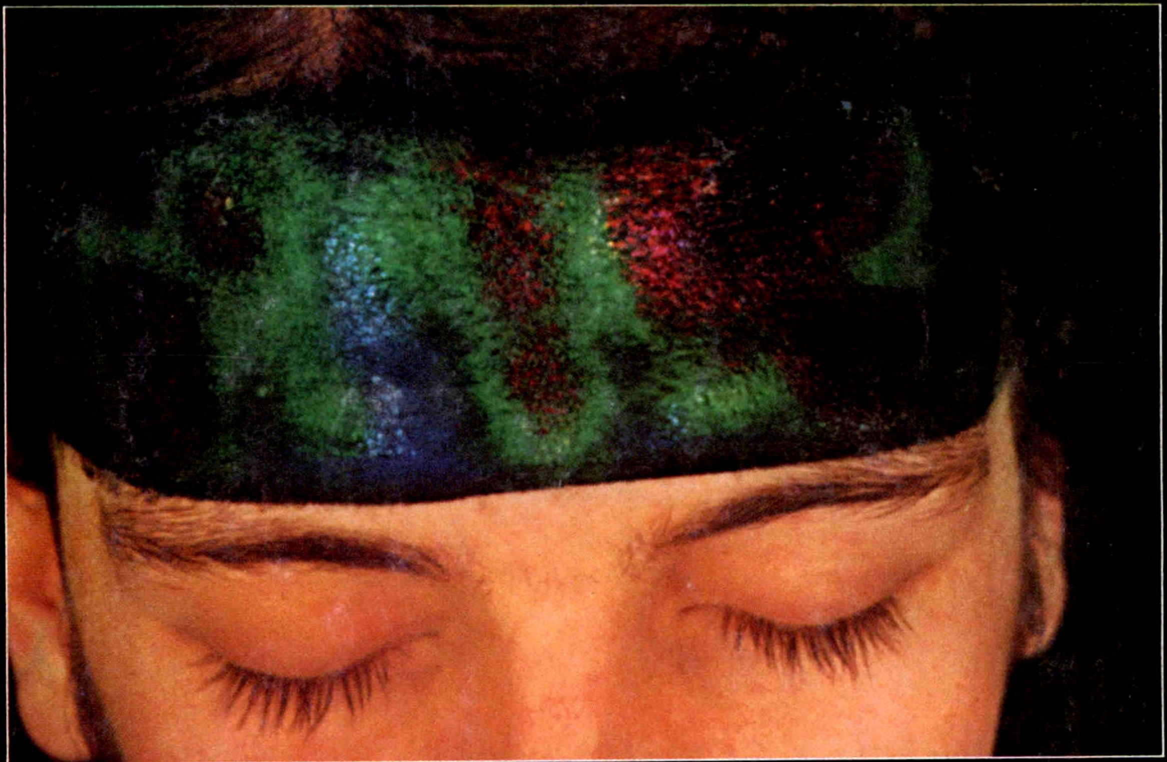

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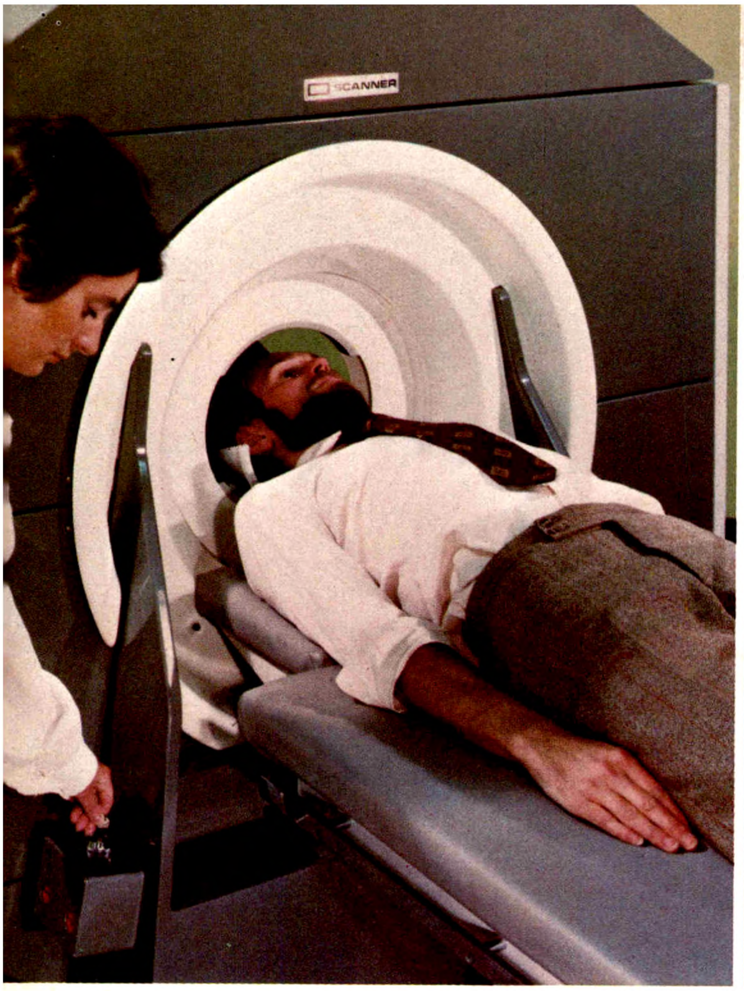

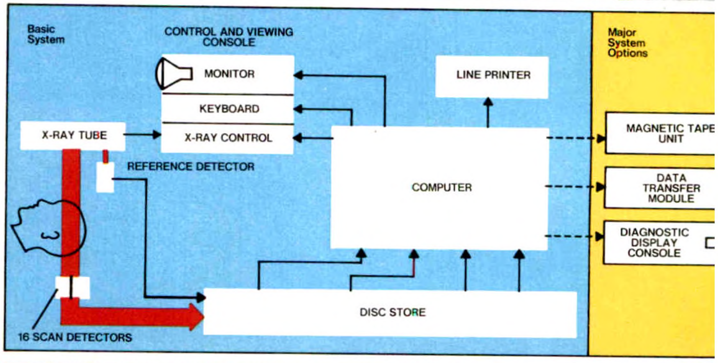

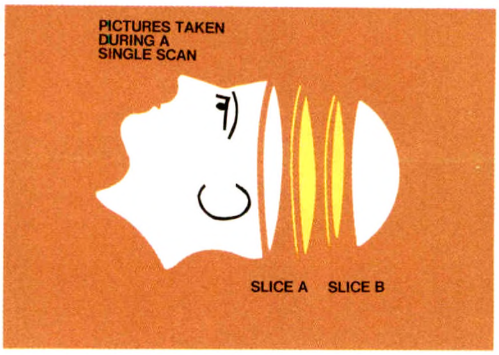
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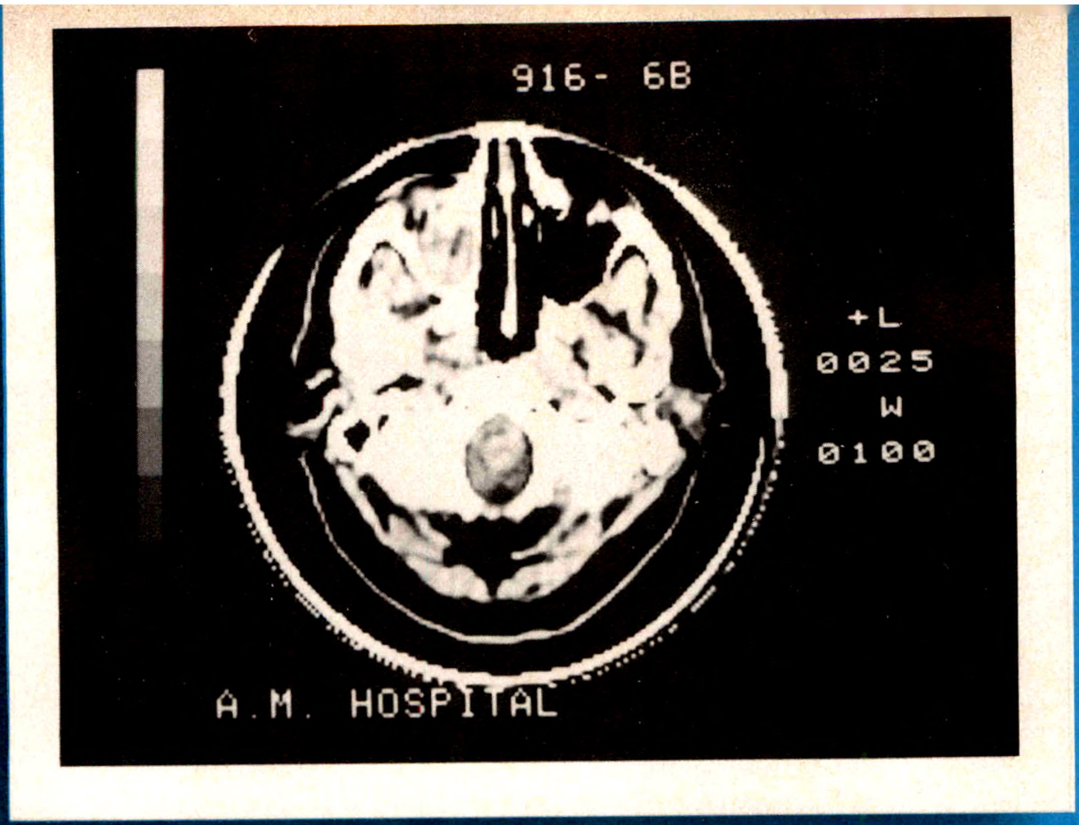

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The vulnerable ages

The first epileptic seizure is most likely to occur during early childhood and at the onset of puberty

About 9 out of 10 epileptics experience their first seizure before the age of 20—with the highest incidence between 5 and 7, when children start school, and at the onset of puberty, a time of physiological and psychic turmoil.[1] The most common type, grand mal, occurs in approximately 75% of epileptic children,[1] and more than 50% of patients who suffer initially from petit mal develop grand mal seizures before they reach the age of 16.[2]

Mysoline (primidone) for control of grand mal, psychomotor and focal epilepsy

At the onset and afterwards— used alone or as concomitant therapy, MYSOLINE may reduce the frequency and severity of major motor seizures—or even eliminate them. *Excellent* for control of grand mal. Valuable for control of psychomotor[1,3,4] and focal epilepsy as well.[5]

Add Mysoline when control with other anticonvulsants is inadequate—As concomitant therapy, MYSOLINE can improve seizure control in grand mal and psychomotor epilepsy. The combined use of phenobarbital, diphenylhydantoin, and MYSOLINE may have additive anticonvulsant effects without additive side effects.[6]

Change to Mysoline when other anticonvulsants fail— A changeover to MYSOLINE is frequently warranted when other anticonvulsants must be discontinued because of important side effects, or when grand mal seizures are refractory to phenobarbital, with or without diphenylhydantoin.[7]

Ayerst®

Mysoline®
(primidone)

Tablets 250 mg.
50 mg.
Suspension 250 mg./5 cc.

May be the start of a better life for the epileptic

See following page of advertisement for prescribing information.

7538

Mysoline® (primidone)

may be the start of a better life for the epileptic

initial and maintenance therapy for
grand mal, psychomotor and focal epilepsy

BRIEF SUMMARY
(For full prescribing information, see package circular.)

MYSOLINE® Brand of PRIMIDONE

Anticonvulsant

ACTIONS: MYSOLINE acts on the central nervous system to raise seizure threshold or alter seizure pattern. The mechanism(s) of action of anticonvulsant drugs is not known.

Primidone has anticonvulsant activity *per se.* In addition, its two metabolites possess anticonvulsant qualities. The major metabolite is phenylethylmalonamide (PEMA); the other is phenobarbital. In addition to its own anticonvulsant potential, PEMA potentiates phenobarbital.

INDICATIONS: MYSOLINE, either alone or used concomitantly with other anticonvulsants, is indicated in the control of grand mal, psychomotor, and focal epileptic seizures. It may control grand mal seizures refractory to other anticonvulsant therapy.

CONTRAINDICATIONS: Primidone is contraindicated in: 1) patients with porphyria and 2) patients who are hypersensitive to phenobarbital (see ACTIONS).

WARNINGS: The abrupt withdrawal of antiepileptic medication may precipitate status epilepticus.

The therapeutic efficacy of a dosage regimen takes several days before it can be assessed.

Use in pregnancy: Recent reports strongly suggest an association between the use of anticonvulsant drugs by women with epilepsy and an elevated incidence of birth defects in children born to these women. Reference has been made to primidone in several cases in which it was used *in combination* with other anticonvulsants; but its teratogenicity has not been conclusively demonstrated. The possibility exists that other factors, *e.g.,* genetic factors or the epileptic condition, may contribute to the higher incidence of birth defects. The data also indicate that the great majority of mothers receiving anticonvulsant medication deliver normal infants.

Anticonvulsant drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and risk to both mother and the unborn child.

When the nature, frequency, and severity of the seizures do not pose a clear threat to the patient, good medical practice requires that the physician weigh the expected therapeutic benefit of anticonvulsant therapy against possible risk on an individual basis.

Neonatal hemorrhage, with a coagulation defect resembling vitamin K deficiency, has been described in newborns whose mothers were taking primidone and other anticonvulsants. Pregnant women under anticonvulsant therapy should receive prophylactic vitamin K_1 therapy for one month prior to, and during, delivery.

The physician should weigh all of the foregoing considerations when treating and counseling epileptic women of childbearing potential.

PRECAUTIONS: The total daily dosage should not exceed 2 Gm. Since MYSOLINE therapy generally extends over prolonged periods, a complete blood count and a sequential multiple analysis-12 (SMA-12) test should be made every six months.

In nursing mothers: There is evidence that in mothers treated with primidone, the drug appears in the milk in substantial quantities. Since tests for the presence of primidone in biological fluids are too complex to be carried out in the average clinical laboratory, it is suggested that the presence of undue somnolence and drowsiness in nursing newborns of MYSOLINE-treated mothers be taken as an indication that nursing should be discontinued.

ADVERSE REACTIONS: The most frequently occurring early side effects are ataxia and vertigo. These tend to disappear with continued therapy, or with reduction of initial dosage. Occasionally, the following have been reported: nausea, anorexia, vomiting, fatigue, hyperirritability, emotional disturbances, sexual impotency, diplopia, nystagmus, drowsiness, and morbilliform skin eruptions. Occasionally, persistent or severe side effects may necessitate withdrawal of the drug. Megaloblastic anemia may occur as a rare idiosyncrasy to MYSOLINE and to other anticonvulsants. The anemia responds to folic acid, 15 mg. daily, without necessity of discontinuing medication.

DOSAGE AND ADMINISTRATION: The average adult dose is 0.75 to 1.5 Gm. per day. The initial dose is 250 mg. Increments of 250 mg. are added, usually at weekly intervals, to tolerance, or therapeutic effectiveness, up to daily doses not exceeding 2.0 Gm. A typical dosage schedule for the introduction of MYSOLINE (primidone) is as follows:

Adults and Children Over 8 Years of Age

1st Week 250 mg. daily at bedtime	*2nd Week* 250 mg. b.i.d.
3rd Week 250 mg. t.i.d.	*4th Week* 250 mg. q.i.d.

In children under 8 years of age, maintenance levels are established by a similar schedule, but at one-half the adult dosage. It is best to begin with 125 mg., with gradual weekly increases of 125 mg. a day, to a daily total usually between 500 mg. and 750 mg.

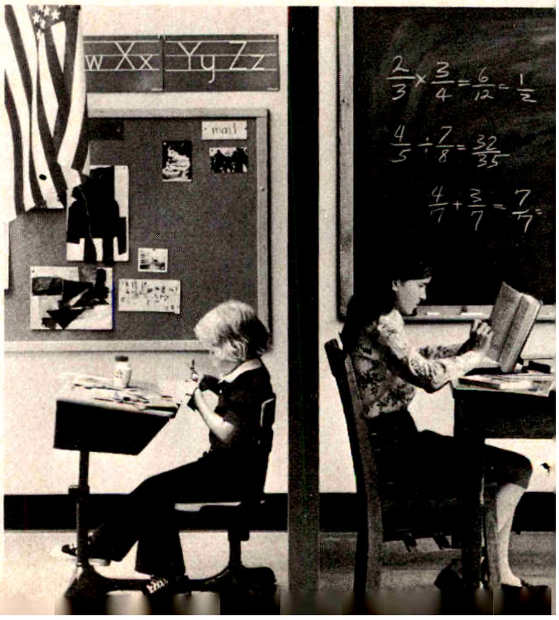
In patients already receiving other anticonvulsants: MYSOLINE should be gradually increased as dosage of the other drug(s) is maintained or gradually decreased. This regimen should be continued until satisfactory dosage level is achieved for combination, or the other medication is completely withdrawn. When therapy with this product alone is the objective, the transition should not be completed in less than two weeks.

MYSOLINE 50 mg. Tablet can be used to practical advantage when small fractional adjustments (upward or downward) may be required, as in the following circumstances:

- for initiation of combination therapy
- during "transfer" therapy
- for added protection in periods of stress or stressful situations that are likely to precipitate seizures (menstruation, allergic episodes, holidays, etc.)

HOW SUPPLIED: MYSOLINE *Tablets*—No. 430—Each tablet contains 250 mg. of primidone (scored), in bottles of 100 and 1,000. Also in unit dose package of 100. No. 431—Each tablet contains 50 mg. of primidone (scored), in bottles of 100 and 500. MYSOLINE *Suspension*—No. 3850—Each 5 cc. (teaspoonful) contains 250 mg. of primidone, in bottles of 8 fluidounces.

References: 1. Livingston, S.: Comprehensive Management of Epilepsy in Infancy, Childhood and Adolescence, Springfield, Ill., Charles C Thomas, 1972, pp. 6, 7, 584. 2. Grossman, H.J.: Ill. Med. J. *135*:260 (Mar.) 1969. 3. Scholl, M.L., in Conn, H.F.: Current Therapy 1973, Philadelphia, Saunders, 1973, pp. 675-7. 4. Metrick, S.: C.M.D. *37*:49 (Jan.) 1970. 5. Forster, F.M.: Med. Clin. North Am. *47*:1579 (Nov.) 1970. 6. White, P.T.: Wis. Med. J. 68:178 (Apr.) 1969. 7. Millichap, J.G.: Drug Ther. *1*:15 (Oct.) 1971.


Ww Xx Yy Zz
$\frac{2}{3} \times \frac{3}{4} = \frac{6}{12} = \frac{1}{2}$
$\frac{4}{5} \div \frac{7}{8} = \frac{32}{35}$
$\frac{4}{7} + \frac{3}{7} = \frac{7}{7} =$

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Lumbar Puncture Tray

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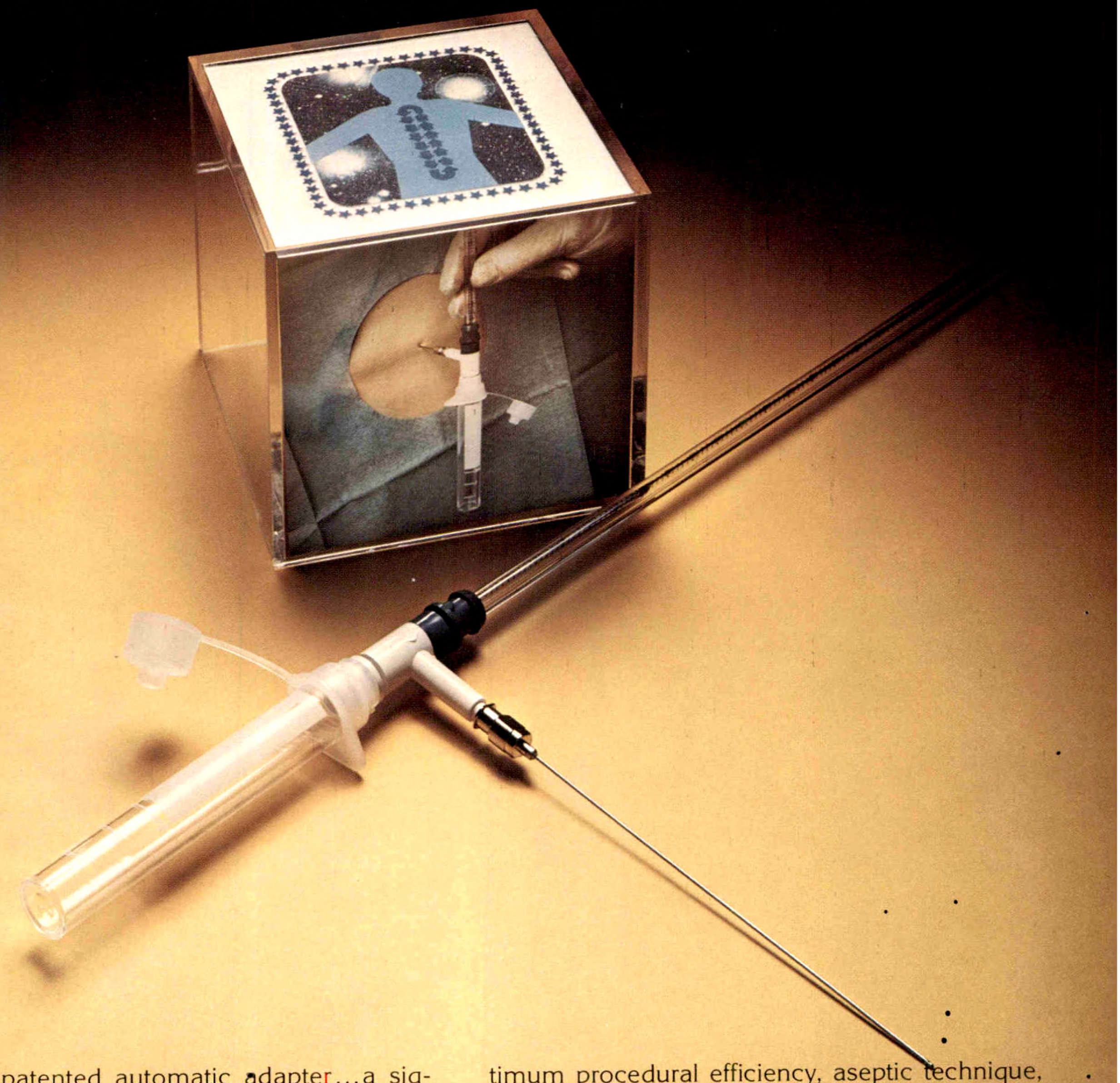

A unique patented automatic adapter…a significant innovation over the old-fashioned 3-way stopcock in measuring fluid pressure and collecting fluid samples.

The adapter contains special self-sealing valves which open once the manometer or specimen vials are attached. The valves also close automatically when the manometer or specimen vials are disconnected. No additional manipulation is required; the entire procedure functions as a closed, aseptic system.

The CURITY Lumbar Puncture Trays provide the highest quality components to ensure optimum procedural efficiency, aseptic technique, and added safety. Five lumbar puncture trays are available to meet adult, pediatric, and infant requirements. CURITY Lumbar Puncture Trays …another new horizon in CURITY diagnostics.

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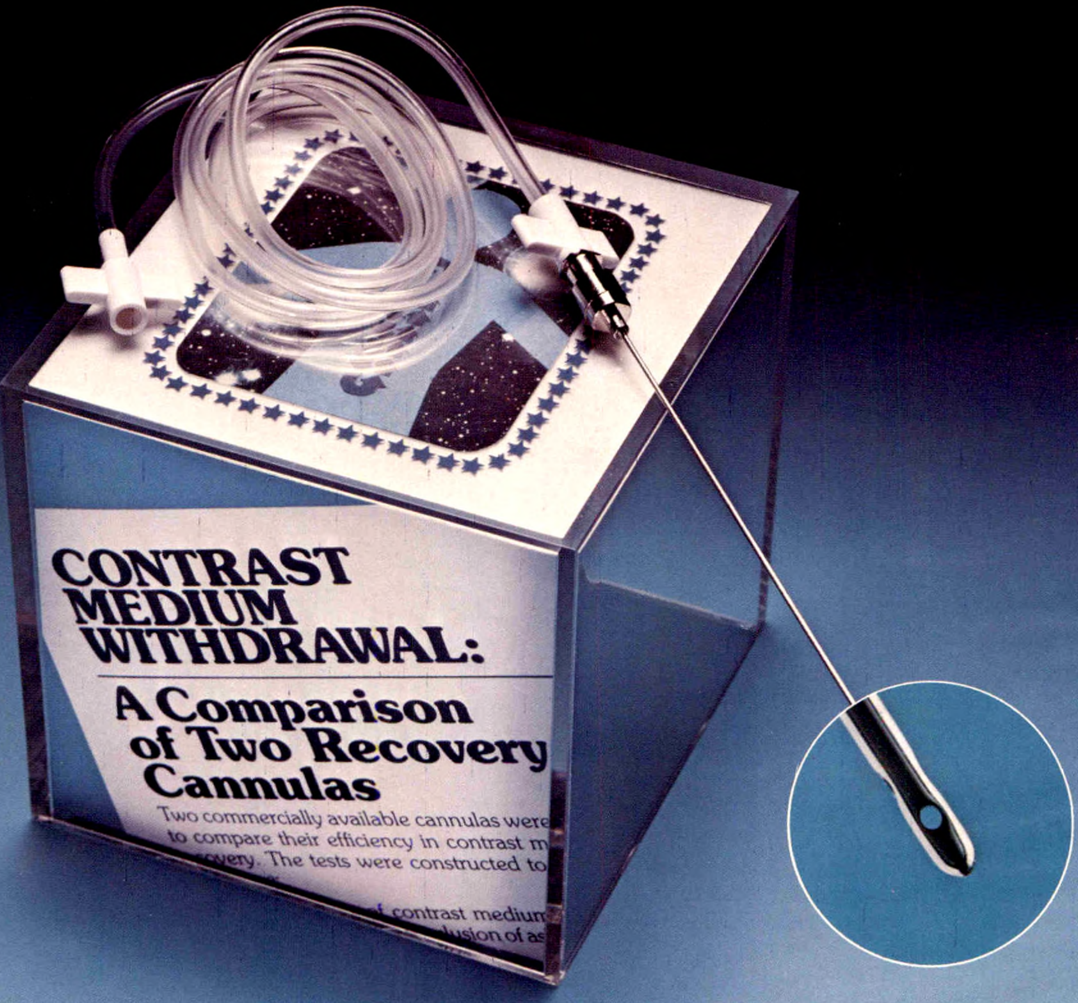
CURITY®
Myelogram Trays

Specially Designed Cannula For Maximum Recovery of Pantopaque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A Comparison of Two Recovery Cannulas
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covery. The tests were constructed to
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An exclusive system...with a specially designed low-hole profile cannula that increases recovery of pantopaque, and in addition minimizes CSF loss. The specially designed cannula slips through the spinal needle and extends beyond the sharpened tip of the needle. The cannula has a smooth blunt end and minimizes the risk of piercing a nerve or puncturing the canal floor. Result—A significantly greater quantity of pantopaque withdrawal!

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Manuscript Preparation.—Submit an original typescript and two high-quality copies of the entire manuscript. All copy (including references, legends, and tables) must be typed double-spaced on 22 × 28-cm (8½ × 11-inch), heavy-duty white bond paper. Ample margins should be provided.

Refer to patients by number (or, in anecdotal reports, by fictitious given names). Real names or initials should not be used in the text, tables, or illustrations.

Titles.—Titles should be short, specific, and clear. They should not exceed 42 characters per line, including punctuation and spaces, and be limited to two lines, if possible.

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Illustrations in full color are accepted for publication if the editors believe that color will add significantly to the published manuscript. The Archives will pay part of the expense of reproduction and printing color illustrations, the remainder to be borne by the author or his sponsor. After deducting the Archives contribution, the author's share is $275.00 for up to six square-finished illustrations that can be arranged on a one-page layout. Any additional illustrations or special effects will be billed to the author at cost. Positive color transparencies (35 mm preferred) must be submitted for an evaluation. Do not send color prints unless accompanied by original transparencies. All transparencies should be carefully packed and sent with the manuscript.

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Photographic Consents.—A letter of consent must accompany all photographs of patients in which a possibility of identification exists. It is not sufficient to cover the eyes to mask identity.

Acknowledgments.—Illustrations from other publications must be acknowledged. Include the following when applicable: author(s), title of article, title of journal or book, volume number, page(s), month, and year. The publisher's permission to reprint should be submitted to the Archives after the manuscript has been formally accepted.

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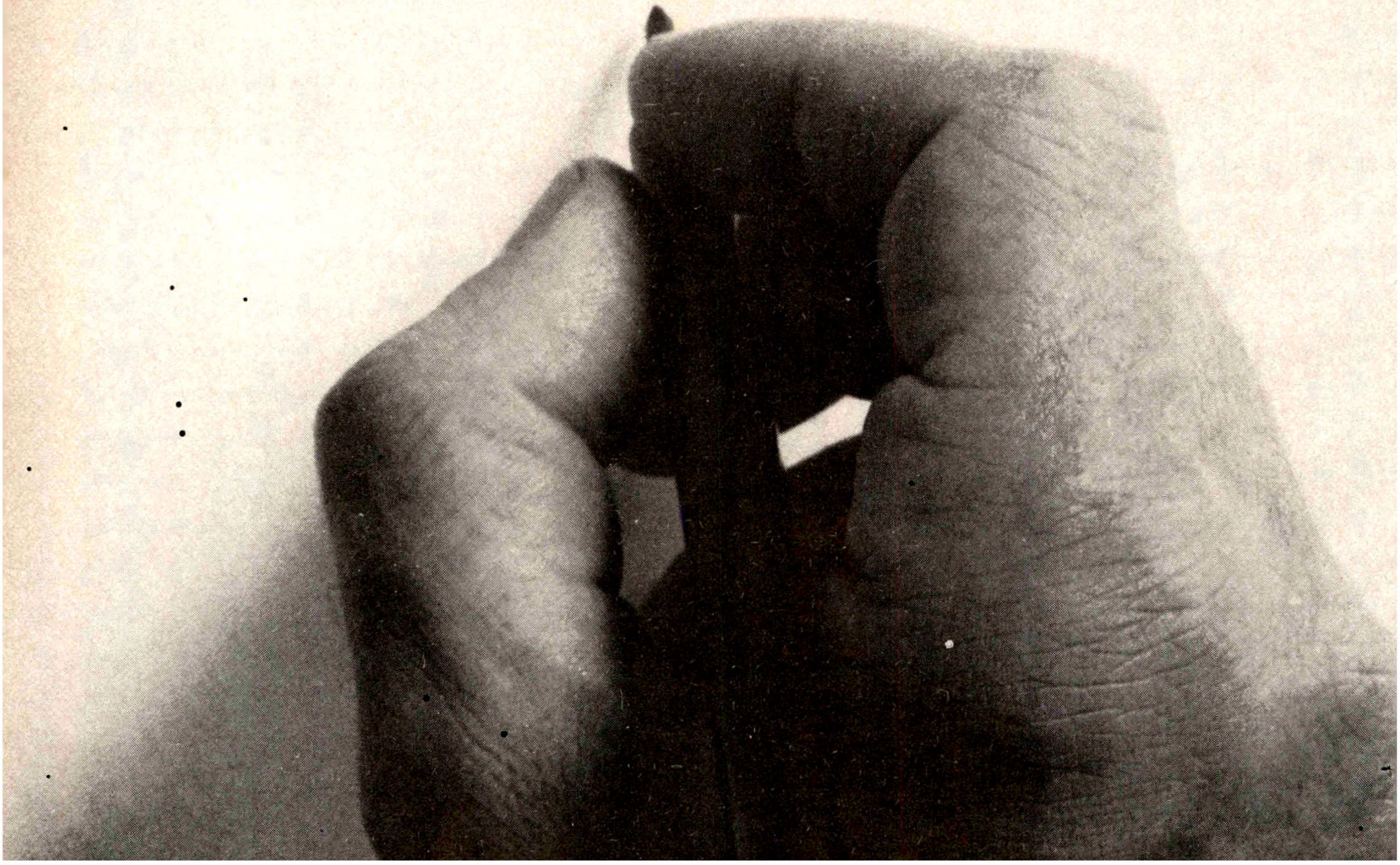
When drug-induced extrapyramidal symptoms complicate therapy



TABLETS: 0.5 mg, 1 mg, 2 mg INJECTION: 1.0 mg/ml

COGENTIN®

(BENZTROPINE MESYLATE | MSD)

highly effective against phenothiazine-induced extrapyramidal symptoms

(except tardive dyskinesia)

often permits needed chemotherapy to continue by controlling drug-induced extrapyramidal manifestations such as: *tremor, akathisia, motor restlessness, muscular rigidity, drooling, dystonic reactions.*

In some patients, however, the phenothiazine dosage may have to be reduced or discontinued. After one or two weeks, COGENTIN should be withdrawn to determine the continued need for it.

When given concomitantly with phenothiazines or other drugs with anticholinergic activity, patients should be advised to report gastrointestinal complaints promptly; paralytic ileus, sometimes fatal, has occurred in patients taking anticholinergic-type antiparkinsonism drugs, including COGENTIN, in combination with phenothiazines and/or tricyclic antidepressants.

Contraindications: Children under three years of age; use cautiously in older children.

Warnings: Safe use in pregnancy not established. May impair mental and/or physical abilities required for performance of hazardous tasks, such as operating machinery or driving a motor vehicle. When given concomitantly with phenothiazines or other drugs with anticholinergic activity, patients should be advised to report gastrointestinal complaints promptly; paralytic ileus, sometimes fatal, has occurred in patients taking anticholinergic-type antiparkinsonism drugs, including COGENTIN, in combination with phenothiazines and/or tricyclic antidepressants.

Precautions: Because of cumulative action, continued supervision is advisable. Closely observe patients with tendencies to tachycardia and those with prostatic hypertrophy. Dysuria may occur, but rarely becomes a problem. Large doses may cause complaints of weakness and inability to move particular muscle groups, requiring dosage adjustment.

Mental confusion and excitement may occur with large doses, or in susceptible patients; visual hallucinations reported occasionally. May intensify mental symptoms when used to treat extrapyramidal disorders due to neuroleptic drugs (e.g., phenothiazines) in patients with mental disorders; in such patients, increased doses of antiparkinsonian drugs can precipitate toxic psychosis; observe patients carefully, especially at the beginning of treatment or if dosage is increased. Tardive dyskinesia may appear in some patients on long-term therapy with phenothiazines and related agents, or may occur after therapy with these drugs has been discontinued; antiparkinsonism agents do not alleviate symptoms of tardive dyskinesia, and in some instances may aggravate them. COGENTIN is not recommended in tardive dyskinesia.

May produce anhidrosis; give with caution during hot weather, especially to the old, the chronically ill, the alcoholic, those who have central nervous system disease, those who do manual labor in a hot environment, and those with disturbances in sweating. If anhidrosis appears, reduce dosage so that ability to maintain body heat equilibrium is not impaired. Occurrence of glaucoma is a possibility; probably should not be used in angle-closure glaucoma.

Adverse Reactions: Adverse reactions may be anticholinergic or antihistaminic. Dry mouth, blurred vision, nausea, nervousness may develop. If dry mouth causes difficulty in swallowing or speaking, or loss of appetite and weight, reduce dosage, or discontinue drug temporarily. Vomiting occurs infrequently and may be controlled by temporary discontinuation, followed by resumption at a lower dosage. Constipation, numbness of the fingers, listlessness, and depression may develop. Occasionally, an allergic reaction, e.g., skin rash, develops; sometimes this can be controlled by reducing dosage, but occasionally requires discontinuation.

Note: Large doses generally cannot be tolerated by older patients and thin patients. Patients with a poor mental outlook are usually poor candidates for therapy. Do not terminate other antiparkinsonism agents abruptly; reduce gradually. When benztropine mesylate is used with levodopa the usual dose of each may need to be reduced.

How Supplied: Tablets in three strengths: 0.5 mg and 1 mg benztropine mesylate in bottles of 100, 2 mg benztropine mesylate in bottles of 100 and 1000, and 1 mg and 2 mg in single-unit packages of 100; Injection, in 2-ml ampuls, containing per ml: 1.0 mg benztropine mesylate, 9.0 mg sodium chloride, and water for injection q.s.

For more detailed information, consult your MSD representative or see full prescribing information. Merck Sharp & Dohme, Division of Merck & Co., INC., West Point, Pa. 19486

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addendum

Facts about dosage schedules of COGENTIN (Benztropine Mesylate | MSD)

In treating extrapyramidal symptoms due to neuroleptic drugs, such as phenothiazines and butyrophenones, the recommended dosage of COGENTIN is 1 to 4 mg once or twice a day orally or parenterally. Dosage must be individualized according to the need of the patient. Some patients require more than recommended; others do not need as much. The tablet form should be used when patients are able to take oral medication.

When extrapyramidal symptoms develop soon after initiation of treatment with neuroleptic drugs, they are likely to be transient. One to 2 mg COGENTIN orally two or three times a day usually provides relief within one or two days. After one or two weeks, COGENTIN should be withdrawn to determine the continued need for it. If symptoms recur, COGENTIN can be reinstituted.

Certain extrapyramidal disorders that develop slowly may not respond to COGENTIN. COGENTIN is not recommended in tardive dyskinesia.

For more detailed information, see full prescribing information.

THIRD

ANNUAL COURSE

Practical Use and Recent Advances in

COMPUTERIZED BRAIN TOMOGRAPHY

BROWARD GENERAL MEDICAL CENTER
Bahia Mar—Fort Lauderdale, Florida
February 17th, 18th, 19th, 1977

Guest Faculty Includes:

Mokhtar Gado, M.D. Chief, Neuroradiology Section, The Edward Mallinckrodt Institute of Radiology, St. Louis, Missouri

Romeo Ethier, MD., Director, Department of Radiology, Montreal Neurological Institute, Montreal, Quebec

Otis Wayne Houser, M.D., Department of Radiology, Mayo Clinic, Rochester, Minnesota

Albert V. Messina, M.D., Assistant Professor of Radiology, Cornell University Medical College

Topics Covered:

1. **Brain tumors**—primary and metastatic.
2. Vascular disease—"stroke syndromes", and subarachnoid hemorrhage.
3. Craniocerebral trauma.
4. Demyelinating disease.
5. Radiation changes.
6. CT Scan of the spinal cord.
7. Recent developments, instrumentation and retrieval of CT Data.

Workshop with live use of EMI-Brain Scanner
Instruction will be available.

-ENROLLMENT LIMITED TO 200-

Registration fee $200.00

Includes elegant banquet and dance

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EMI-Scan Group
Neurological Sciences Building
300 S.E. 17th Street
Fort Lauderdale, Florida 33316
Phone: (305) 524-6527

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SCHOOL OF MEDICINE

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TAMARRON
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FEBRUARY 9, 10, 11, 1977

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This course will include lectures and seminar sessions covering basic disorders of ocular motility and the visual system. Ample time, between sessions, has been provided for leisure activity at Tamarron and the Purgatory Ski Area.

Tuition: $200.00. Resident Tuition: $100 upon application by their department head.

Registration is limited. Make check payable to:

ROCKY MOUNTAIN NEURO-OPHTHALMOLOGY COURSE
DEPARTMENT OF NEUROLOGY
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Postgraduate course

CLINICAL ADVANCES IN PEDIATRIC NEUROLOGY

November 8 and 9, 1976

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MILWAUKEE CHILDREN'S HOSPITAL

Guest Faculty:

Paul Dyken
John Freeman
Isabelle Rapin
Kenneth Swaiman

Topics:
Neonatal seizures, new anticonvulsants, muscular dystrophies, learning disorders, delayed speech, a practical diagnostic approach to mental retardation.

Approved for 13 hours of prescribed credits by the American Academy of Family Physicians and 13 hours AMA Category I credits.

Contact:

Jerome V. Murphy, M.D.,
Director of Pediatric Neurology
Milwaukee Children's Hospital
Milwaukee, WI 53233

A New Editor for the ARCHIVES

The *Archives of Neurology* first appeared in 1919 as the *Archives of Neurology and Psychiatry*. Since 1959 it has been published under its current title. Through the years it has had a distinguished record and a succession of highly respected and capable editors. Since its inception, this publication was the official journal of the American Neurological Association (ANA) as well as being an official publication of the American Medical Association.

In June 1976, the ANA officially withdrew its support from the ARCHIVES and now plans to publish its own independent journal.

The AMA wishes the ANA well in its new endeavor, but believes the ARCHIVES should continue to be published in order to provide a medium for the publication of clinical papers in the fields of medical neurology, neurosurgery, and neuroradiology.

The AMA welcomes Maurice W. Van Allen, MD, as the new editor of the ARCHIVES.

Doctor Van Allen is a graduate of the University of Iowa School of Medicine. He interned at the Pennsylvania Hospital, and completed his professional training as a member of the armed forces. He became Board certified in neurological surgery in 1954 in neurology in 1963.

Since 1952 he has held academic appointments at the University of Iowa, and in 1974 was appointed head of the Department of Neurology, College of Medicine, University of Iowa.

We feel confident that under Dr Van Allen's editorship, the ARCHIVES will continue to fill an important place in scientific publishing.

WILLIAM R. BARCLAY, MD

Perspectives and Plans

We are in an exciting and challenging period of advance in the clinical neurosciences. Computerized axial tomography will surely rank with pneumography and angiography as a landmark contribution to neurologic diagnosis. Elucidation of the enzymatic defects responsible for certain heritable diseases continues, with substantial promise for definitive management. Increased understanding of the nature and role of neurotransmitters has created the basis for targeted pharmacologic therapy. Pathogenesis of the demyelinating diseases may be finally revealed through study of disordered immunologic response. Behavioral neurology has increased the knowledge of cortical function. The application of new techniques of radiographic localization and of regional blood flow with increasingly sophisticated tests of function will further complement and extend the studies of experimental work.

Other advances have led to enhanced care in current clinical application. The determination of anticonvulsant drug levels has substantially improved control of epilepsy. The use of antifibrinolytic agents has resulted in an important reduction in morbidity and mortality in the early course of ruptured intracranial aneurysm. Neurosurgical skills are increasingly refined.

The growth of the specialty and the discipline has been rapid and gratifying. Federal support of training and research in clinical neurology and allied disciplines has been a very profitable investment. However, this growth has created two problems for the specialty that require attention and deserve comment.

The training programs have graduated a new body of practicing neurologists who do not as yet have a sense of needed cohesiveness in their specialty nor of strong continued ties to their mentors. This is in part because of still limited numbers and in part because chiefs of training programs are preoccupied with teaching, research, and administrative responsibilities.

The *Archives of Neurology* will attempt to increase the sense of specialty identity and cooperative action. It will foster the interaction of practitioners who represent and support the specialty and academicians who must renew and broaden the discipline.

Some change in emphasis toward this end may be anticipated. Increased attention will be given to the problems and expressions of practitioners. The ARCHIVES must serve them as they in turn serve the public. Authoritative reviews will be encouraged. The sections of the ARCHIVES devoted to letters, comments, and clinical notes are an excellent medium for expanded discourse on current problems of practice and care. These sections will be modified to serve as a sounding board. But they must depend on the readership for sustained interest and value. At the same time the enviable reputation of the ARCHIVES as a medium for publication of valuable original contributions must be maintained.

The other problem of the specialty relates to the very nature of the nervous system and its disorders. With each year the nervous system is less and less perceived as existing in comfortable isolation from the rest of the body and with each year those who specialize in the study and treatment of nervous disorders are less isolated from their colleagues in other specialties and may be less comfortable. Neurologists and neurosurgeons who once fancied themselves sitting atop both specialty and discipline, envied for esoteric knowledge most, now admire and use the contributions to research, diagnosis, and therapy made by nonneurologic colleagues.

Hence an effort must be made to avoid fragmentation in expansion and to pull together diverging tendencies. The integrity of the most demanding of clinical pursuits must be protected by its teachers and practitioners. The diagnostic expertise and insight that follow only from good teaching, abiding interest, hard work, long experience in the clinic, and a solid foundation in the basic neurosciences can be substantially enhanced but not replaced by new technology and by the help of other experts. What better way to ensure this integrity than to draw together and invite contributions from our colleagues who share our fascination with the nervous system? Let us mold their contributions with our own and with those of our surgical companions.

The American Medical Association, now the sole sponsor of the ARCHIVES, has had a long and distinguished role in professional and public service. A most important aspect of this service has been the subsidized publication of a series of specialty journals, including the *Archives of Neurology*. This remarkable boon has been taken for granted as a public utility. (The debt that all of us owe the AMA has been, unfortunately, largely ignored.) We now anticipate a continued beneficient relationship as we concentrate on the content of an outstanding journal.

The continued and increased support of the entire neurologic community and the related specialties is solicited in our efforts.

MAURICE W. VAN ALLEN, MD

Original Contributions

Disease Markers in Acute Multiple Sclerosis

Peter C. Dowling, MD, Stuart D. Cook, MD

• Three serum components that are known to become elevated during inflammation and tissue destruction, C-reactive protein, C3 proactivator, and orosomucoid, which are acute phase reactants, and serum IgM were measured in patients with multiple sclerosis (MS) hospitalized with acute exacerbations. Significantly elevated levels of one or more of these serum components were found in 12 of 13 patients with clinically active MS. Serial studies in two patients revealed that clinical improvement was accompanied by a decline in the serum levels of these factors. These findings suggest that measurement of these serum proteins may be of value in assessing progress of disease activity in MS patients.

(*Arch Neurol* 33:668-670, 1976)

Physicians attempting to judge the progress of multiple sclerosis (MS) are handicapped by the intermittent clinical course of the illness and the fact that the disease may be actively progressing in the absence of new signs. This report deals with one of a series of studies that have been undertaken in this laboratory to find a simple serologic method for determining disease activity in MS.

SUBJECTS AND METHODS

Serologic findings on 13 highly selected cases from our series of nearly 60 patients with MS are reported in this retrospective study. These subjects were acutely ill and hospitalized with clinical findings consistent with active demyelinating disease of central origin. The first blood sample was collected within two weeks of exacerbation. Subjects with secondary complications such as decubitus ulcers, respiratory, or genitourinary tract infections were excluded.

Patients were divided into two groups, based on the likelihood of a firm diagnosis of MS finally being established. The first ten cases listed in Table 1 are considered definite MS, based on generally accepted criteria.[1] The diagnosis of MS was subsequently confirmed by autopsy in case 3, and two other individuals in this category have become tissue-proven cases (one by autopsy, one by biopsy). The last three cases listed in Table 1 also had a remitting deficit of central origin (mainly visual abnormalities) but no clinical evidence for a second lesion up to the present.

During remission, both groups of patients had little remaining neurologic deficit. Twelve were ambulatory following discharge and during the period of this study, only one required a wheelchair.

Serum samples from earlier cases in this series were stored at −20 C. More recently obtained samples were kept at −80 C. Levels of four serum proteins—three acute phase reactants (C-reactive protein [CRP], C3 proactivator [C3PA] measured as C3 activator, and orosomucoid) and immunoglobulin M (IgM) were quantitated by single radial immunodiffusion (Behring diagnostics).[2] To assess reliability of assays, a sample of known concentration was included on each immunodiffusion plate. Confidence values for the test of ± 8% were required. Our normal values ± 2 standard deviations are in close agreement with the literature for these serum proteins.[3-5] Controls consisted of ten normal sera stored at −20 C for the same period of time and 30 additional normal sera of more recent origin. In two instances where numerous serial samples were obtained on the same MS patient, the patient's own blood was able to serve as an important additional control.

RESULTS

Table 2 shows levels of the four serum proteins in 13 acutely ill MS patients. A substantial number (70%) of patients had positive CRP reactions in their serum. C-reactive protein is unique among acute phase reactants in not being normally present in the bloodstream. Serum levels of two other acute phase reactants, C3PA and orosomucoid, were each substantially elevated in more than half of the subjects when compared with a large group of normals. Serum IgM levels were also increased in nearly one half of the patients. Table 3 shows time course studies in two cases in which repeated serum samples were obtained over a long time period. Clinical recovery was associated with a substantial decline in the level of these serum proteins. The second patient, with acute remitting internuclear ophthalmoplegia, is particularly noteworthy because his initial serum

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Table 1.—Clinical Features

Patient/Age, yr/Sex	Disease Duration, mo	Current Episode	Subsequent Course	Further Episodes*	Major Manifestations	Treatment
1/30/F	24	2nd	Improvement	+	Optic nerve, cerebellum cord	. . .
2/16/M	11	2nd	Improvement	+	Optic nerve, cord	ACTH†
3/29/M	5	1st	Improvement	(+)	Organic mental syndrome, optic nerve, cord	. . .
4/24/F	1	1st	Improvement	+	Brain stem, cord	. . .
5/39/F	12	2nd	Improvement	(+)	Organic mental syndrome, optic nerve, cord	Steroid
6/21/F	4	2nd	Improvement	(+)	Optic nerve, brain stem	. . .
7/30/F	60	4th	Improvement	?	Optic nerve, hemiplegias	ACTH
8/46/F	36	3rd	Improvement	+	Organic mental syndrome, optic nerve, hemiplegia	Steroid
9/27/F	60	2nd	Improvement	+/−	Organic mental syndrome, brain stem	. . .
10/43/F	144	5th	Improvement	?	Optic nerve, bilateral corticospinal	ACTH
11/20/F	1	1st	Improvement	+	Organic mental syndrome, bilateral optic nerve	Steroid
12/21/M	1	1st	Improvement	?	Acute internuclear ophthalmoplegia	. . .
13/21/F	9	2nd	Improvement	?	Bilateral optic nerve	. . .

*Episodes in parentheses represent tissue-proven cases.
†Adrenocorticotropic hormone.

values, while high, were still within the normal range. Follow-up determinations demonstrate the importance of obtaining serum over a long term at weekly intervals, because samples collected during his maximum deficit showed the highest values, which later receded to lower levels. This suggests that if the patients own basal levels are used as controls, important information as to disease activity may be revealed, even with high normal values.

Table 2.—Serologic Data

	C-Reactive Protein	C3 Proactivator, mg/100 ml	Orosomucoid, mg/100 ml	IgM, mg/100 ml
Patient 1	−	36	108	90
2	+	26	114	128
3	+	40	150	312
4	+	21	104	368
5	+	34	138	248
6	+	36	184	440
7	−	29	120	350
8	+	46	164	248
9	+	32	120	250
10	+	26	184	244
11	+	40	160	522
12	−	23	94	220
13	−	25	168	424
Normal* (N = 42)	−	20 ± 11	74 ± 36	188 ± 90
Abnormal	70%†	54%†	77%†	46%‡

*Normal mean values ± 2 standard deviations are shown.
†$P < .001$.
‡$P < .002$.

COMMENT

The main finding in this report is that peripheral blood of acutely ill MS patients frequently contains substantial elevations of CRP, orosomucoid, C3PA, and IgM, which may show a close correlation with disease activity. The first three of these proteins can be considered acute phase reactants. A number of diverse conditions such as neoplasia, trauma, and infectious disease can induce these serologic abnormalities. The common denominator in all these conditions is believed to be tissue destruction or inflammation. Previously, interest in these laboratory guides for assessing disease activity has been limited mainly to rheumatic disease. However, in 1972, Dowling and Cook[6] described increased serum levels of CRP in a number of MS patients. This finding has since been confirmed by Schuller and Allinquant.[7] Of interest is that they could rarely detect CRP in the spinal fluid, which demonstrates the importance of testing blood components. Finding elevated levels of CRP led us to explore the serum from MS patients for two other acute phase reactants, C3PA and orosomucoid.

Evidence that C3PA is a potent acute phase reactant is derived from recent sequential studies on a group of patients following surgery and others with a wide variety of active inflammatory diseases.[5] In that report, C3PA showed the most dramatic increase of the various serum proteins studied. The authors raised the possibility that C3PA, which is an alternate

Table 3.—Relationship of Acute Phase Reactants in Two Patients With Multiple Sclerosis*

	Manifestations	Days	C-Reactive Protein	C3 Proactivator, mg/100 ml	Orosomucoid, mg/100 ml	IgM, mg/100 ml
Patient 8	Acute bilateral optic neuritis and hemiplegia (treatment with steroids)	7	+	46	164	248
		14	+	35	184	120
	Improving	41	–	23	130	80
		70	+	29	178	90
	Essentially normal	270	–	17	88	80
Patient 12	Acute bilateral internuclear ophthalmoplegia	14	–	23	94	220
	Syndrome (no treatment)	21	–	23	94	250
	Essentially normal	30	–	22	86	250
		37	–	17	86	204
		42	–	16	85	204
		49	–	15	66	188
		55	–	14	60	128
		60	–	14	66	170
		67	–	15	78	156
Normal (N = 42)			–	20 ± 11	74 ± 36	188 ± 90

*Serum levels recede with recovery.

pathway complement component, might serve as an additional indicator in certain forms of acute inflammation. Our growing experience reporting serum C3PA elevation in at least two primary demyelinating conditions (MS and the Guillain-Barré syndrome) increasingly supports this possibility.[8] To our knowledge, no report on serum orosomucoid has reached the neurologic literature. In interpreting these findings, it is important to realize that elevations in acute phase reactants are not specific for any disease entity, ie, MS; however, they are quite specific for the presence of ongoing inflammation, whatever the cause.

Only limited studies on serum immunoglobulin abnormalities in MS have been reported. One study found IgG and IgA abnormalities in spinal fluid during the acute phase of disease activity but failed to demonstrate alterations in serum levels.[9] Conspicuously missing from this report was mention of serum IgM levels. In a much larger series on single serum samples, Kuwert and Betrams[10] reported substantially elevated serum IgM levels in certain MS patients. These sera also possessed an unusual cold-reacting autolymphocytotoxin. Kuwert and Betrams[10] further state:

> No patient so far has been tested for cold-reacting auto-lymphocytotoxin activity from the onset of a bout until clinical improvement or until a stationary stage of the disease. No comment can be given concerning the correlation of the antibody activity with the activity of the disease.

Our experience confirms their serum immunoglobulin findings. What is now necessary for further understanding the MS patient is to document exactly what the relationship is between these various circulating substances and disease activity in prospective studies measuring as many indexes as accurately as possible. Through this type of study a more rational approach to therapy, cause and pathogenesis may be achievable.

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Perioptic Meningiomas

Syndrome of Long-Standing Visual Loss, Pale Disk Edema, and Optociliary Veins

Carl Ellenberger, Jr, MD

• Three patients had a syndrome of progressive or long-standing visual loss, pale disk edema, and optociliary veins, indicating that a spheno-orbital meningioma had invaded the anterior perioptic meninges. To diagnose this syndrome, one must distinguish "disk edema" from "papilledema"; although both result from increased pressure within the perioptic subarachnoid space, disk edema is caused by a variety of lesions just behind the globe, whereas papilledema is caused by remote lesions that raise intracranial pressure. Optociliary veins reflect the slowness of progression of both processes. This ophthalmoscopic diagnosis carries important implications, namely, that the tumor grows very slowly and that surgical treatment will not improve vision. Therefore, excision may not be the treatment of choice.

(*Arch Neurol* 33:671-674, 1976)

Spencer[1] and Spencer and Hoyt[2] called attention to the syndrome of long-standing visual loss, pale disk edema, and optociliary veins, a triad of signs indicating spheno-orbital meningioma in the anterior perioptic meninges. This "disk edema" is distinct from "papilledema" and has different, but important, diagnostic and therapeutic implications. The following three case reports illustrate this syndrome, which permits diagnosis of meningioma by ophthalmoscopy.

REPORT OF CASES

Case 1.—A 60-year-old man gradually became blind in the left eye during a year beginning about 12 years before hospitalization. Vision in the right eye remained normal until five years before admission, when gradual loss of visual field, first attributed to glaucoma, began. At about the same time, he began to notice a chronic, dull, bifrontal headache and he became more quiet and passive.

At the time of admission, his vision was 20/30. The left eye did not perceive light. Only the right nasal visual field remained, and its isopters were moderately constricted. The right optic disk appeared pale; the left disk was atrophic, slightly edematous, and surrounded by several deep retinal hemorrhages. The retinal veins did not pulsate. One tortuous venous channel on the temporal side of the optic disk filled with fluorescein that was injected intravenously before the major tributaries of the central retinal vein opacified (Fig 1). The results from the remainder of the neurologic examination were normal.

Radiographic studies indicated a large mass in the region of the planum sphenoidale and tuberculum sellae. The neurosurgeon found a meningioma that stretched the right optic nerve upward and completely encased the left half of the optic chiasm, the left optic nerve, and the left anterior clinoid process. Partial excision of the tumor decompressed the right optic nerve and chiasm and improved vision slightly in the right nasal visual field. The retinal hemorrhages disappeared and the disk edema gradually changed to complete optic atrophy (Fig 2).

Case 2.—A 48-year-old man began to have horizontal diplopia 12 years before admission. After prismatic correction, he no longer had diplopia, but gradually became aware of decreasing vision in the right eye, mild retro-orbital pain, protrusion of the right globe, and slow enlargement of the right side of his forehead and temple. Vision was 20/40 and 20/20. An afferent pupillary defect was noted on the right. All isopters in the right visual field were constricted compared with those on the left, especially in the upper nasal quadrant. Abduction, adduction, and elevation of the right eye were greatly restricted, and forced duction of the globe in these directions met resistance. The right optic disk was pale and edematous; three tortuous optociliary veins had formed (Fig 3). Choroidal folds indicated that the posterior wall of the globe was indented by the expanding tumor. Results of neurologic examination were normal.

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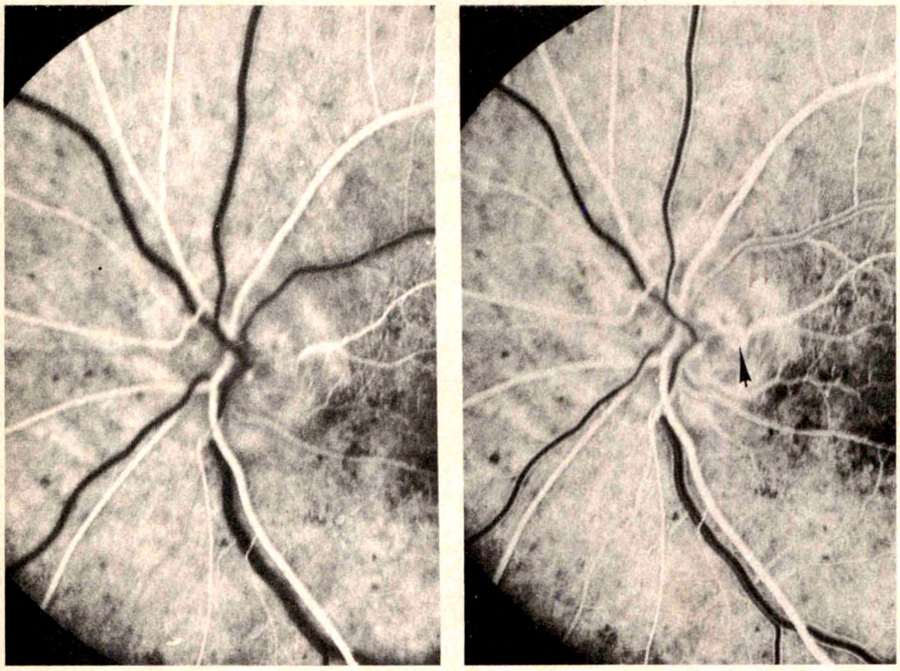


Fig 1.—Left fundus (case 1). Left, Arterial phase. Right, Early venous phase. Note that optociliary vein (arrow) opacifies early, while other major tributaries of central retinal vein are still unfilled by fluorescein.

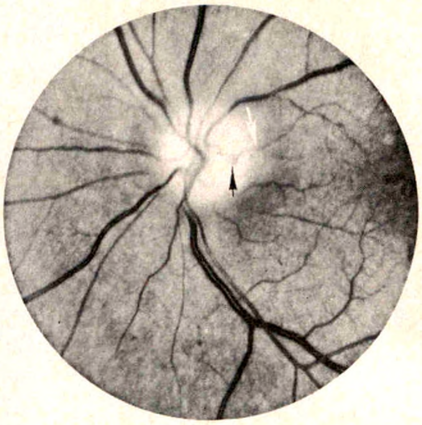


Fig 2.—Atrophic left optic disk (case 1). Black arrow indicates optociliary vein; white arrow, normal cilioretinal artery. Retinal vessels stand out in unusual clarity because ganglion cells of retina are absent.

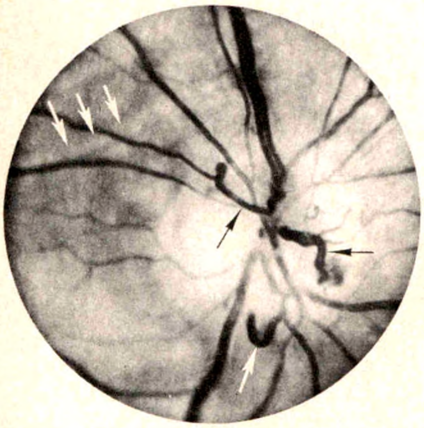


Fig 3.—Right optic disk (case 2). Disk margins are blurred by edema; three optociliary veins on disk are marked by arrows in center and at bottom. Arrows in upper left indicate one of several choroidal folds.

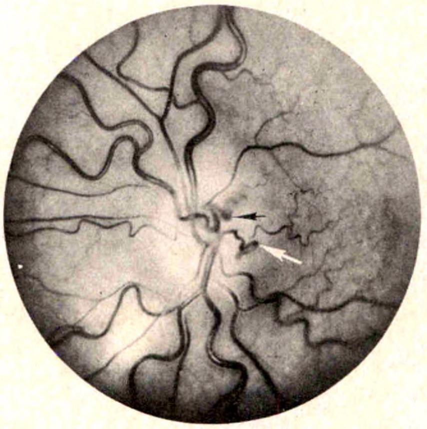


Fig 4.—Left fundus (case 3). Arrows indicate optociliary veins. Retinal vessels are unusually clear because retinal ganglion cells are absent.

Polytomography revealed extensive sclerosis of anterior clinoid process, the lesser wing of the sphenoid bone, and the floor of the sella turcica. The presence of a mass above the medial portion of the right sphenoid wing, characteristic of meningioma, was confirmed by arteriography. Further diagnosis and therapy were not pursued.

Case 3.—A 38-year-old woman had exotropia on the left. Medical history disclosed that she had gradually lost the sight of the left eye during adolescence. Since then, she had been otherwise asymptomatic, except for mild, occasional, retro-orbital aching.

Vision in the right eye was 20/20; the left eye was blind. Pale disk edema and optociliary veins in the left fundus are illustrated in Fig 4. Tomography and carotid arteriography were interpreted as normal at her local hospital. Computerized transaxial tomography (CT), however, showed thickening of the left optic nerve (Fig 5). Additional cross-sectional views showed a small mass at the apex of the orbit that did not extend intracranially.

COMMENT

Three patients had long-standing visual symptoms, ranging in duration from 12 to 25 years, unilateral, pale, disk edema, and prominent retinociliary venous anastomoses on the surface of the optic disk. Despite lack of histopathologic confirmation in cases 2 and 3, their resemblance to cases described in the literature, combined with radiographic abnormalities, led to a firm diagnosis of meningioma.[1-6] In addition, choroidal folds in case 2 and CT scan in case 3 indicate that the tumor extended forward to the back wall of the globe. In cases 1 and 2, an intracranial meningioma extended into the orbit through the optic canal, a common occurrence.[7] In case 3, the early visual loss and lack of evidence of an intracranial mass indicate that the tumor probably began within the optic canal and only extended forward, a less common occurrence.[8,9]

Usually, meningiomas or other expanding lesions adjacent to the anterior visual pathways cause progressive visual loss and optic atrophy.[10] Less often, certain tumors (especially meningioma), leukemia, infection, and carcinoma, invade or originate in the arachnoid sheath of the optic nerve (perioptic meninges) and cause edema of the optic disk as well as atrophy.[1-6,8] Drusen of the optic disk may cause both edema and the development of optociliary veins (Fig 6).[11] Recently, an identical funduscopic abnormality was described in a patient, the fourth in the medical literature, with an arachnoidal cyst in the perioptic meninges immediately behind the globe.[12] Therefore, optociliary veins and pale disk edema are not pathognomonic of meningioma. However, in this case, the visual loss was only two years in duration. In addition, current orbital diagnostic measures, ultrasound, and CT, not done in this patient, should accurately distinguish a solid meningioma from a fluid-filled cyst in most cases.

The combination in case 1 of disk edema in one eye and optic atrophy in the other might be mistaken for the syndrome of Foster Kennedy. However, in this instance, the ophthalmoscopic abnormalities were related to direct compression of the optic chiasm and invasion of one optic nerve sheath and were not due to increased intracranial pressure caused by a tumor on the side of atrophic disk, as Foster Kennedy reported.[13]

Both disk edema and papilledema elevate the optic disk and blur its margins; therefore, in some instances, they may be indistinguishable by ophthalmoscopic examination. In such instances, the remainder of the clinical findings must be used to make the distinction. For example, most patients with disk edema complain of unilateral visual symptoms and have abnormal vision. Patients with papilledema complain of remote neurologic symptoms but have bilateral swollen disks without impaired vision.

The term "disk edema," in current usage, distinguishes elevation of the optic disk and blurring of its margins caused by local lesions in and around the optic nerve from "papilledema," which may appear similar, but denotes a remote effect of increased intracranial pressure.[2] Common to the pathogenesis of both is impaired venous outflow from the prelaminar and retrolaminar portions of the optic nerve that results in hydrostatic dysequilibrium, the pressure in the intravascular compartment exceeding that in the perivascular space. Capillary permeability increases and fluid accumulates in the extracellular prelaminar tissue.[2] The additional factor of ischemia in the swollen nerve restricted by the rigid scleral canal must promote this process, as experimentally, restriction of venous flow alone does not cause changes in the optic disk.[14] Transmission of increased intracranial pressure into the perioptic subarachnoid space causes the hydrostatic dysequilibrium that leads, indirectly, to papilledema. In contrast, various lesions in the anterior part of the optic nerve, such as perioptic tumor, initiate the same process by direct pressure.[2] "Disk edema" is thus a descriptive term, not suggesting cause, as "papillitis" suggests inflammation or infection, for example. The term does indicate, however, that the lesion is in the disk or just behind it.

Fig 5.—Computerized transaxial tomogram of orbits in case 3. Arrow indicates thickened shadow of left optic nerve.

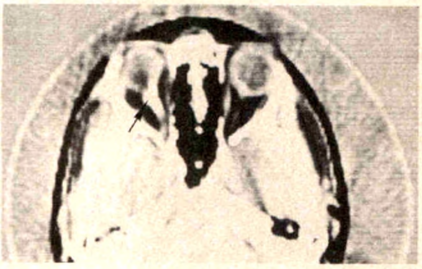


Fig 6.—Elevated, slightly edematous optic disk, presumably containing multiple hidden drusen.[11] Normal peripapillary striations would not be seen with papilledema. Arrow indicates optociliary vein.

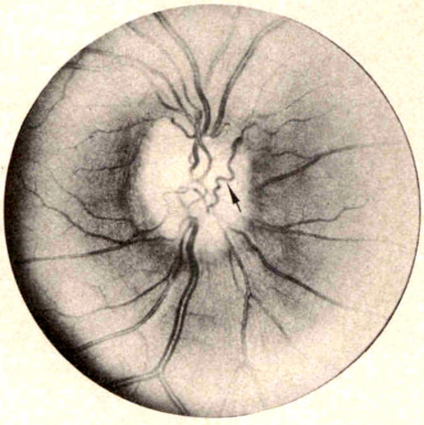
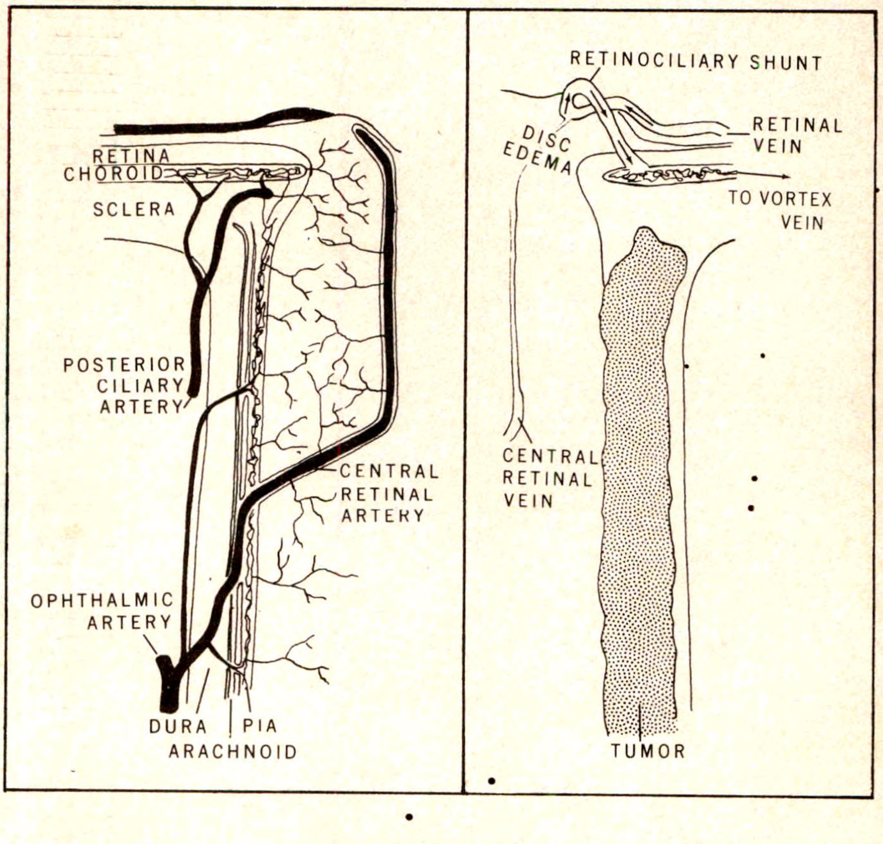


Fig 7.—Horizontal section of human optic nerve. Left side indicates normal arterial circulation; right side, a proposed mechanism for formation of optociliary veins. (Modified from Hogan et al.[15])



Either long-standing disk edema or papilledema may eventually lead to optic atrophy, when no prelaminar tissue remains to accumulate fluid. However, because of the difference in pathogenesis, patients with papilledema are more likely to retain good vision.

Enlarged retinociliary anastomoses, also called "optociliary veins," also indicate a lesion in the anterior perioptic meninges and reflect its chronicity. They represent dilated connections, originally only potential anastomoses, between the two major divisions of the ocular circulation. One division, the ciliary circulation, derives from two or three short, posterior ciliary arteries that branch from the ophthalmic artery before it enters the nerve (Fig 7). The ciliary vessels supply the outer surface of the optic nerve and also the optic disk, choroid, and deeper layers of the retina.[15] The other division, the central retinal artery, supplies the central core of the proximal portion of the optic nerve and inner layers of the retina, but not the optic disk.[15] Occasionally, anastomoses between the central retinal and ciliary circulations can be seen on the optic disk in normal eyes.[16] Much more commonly, a cilioretinal artery, a derivative of the ciliary circulation, pierces the optic disk and supplies a small area of the retina (Fig 2).

Increased pressure within the edematous, prelaminar portion of the optic nerve interferes with venous flow through the central retinal vein, also passing through this unyielding scleral canal. Venous blood therefore follows retinociliary channels of lesser resistance of the edge of the disk and into the ciliary venous system. Then it leaves the globe through the vortex veins closer to the equator of the globe (Fig 7). Eventually, the retinociliary anastomoses enlarge and become visible (Fig 1 through 4). Because the mechanisms of disk edema and papilledema are similar, optociliary vessels may occasionally be seen in long-standing papilledema.

Salzmann[5] was the first to describe abnormal veins on the optic disk of a patient with a perioptic meningioma. He coined the term "optociliary vessels." The protracted course of meningiomas is particularly favorable to their formation. Proof that these channels shunt retinal venous blood into the ciliary circulation was provided by fluorescein angiography.[3]

Recognizing that an intracranial meningioma extends into the anterior perioptic meninges is important for at least two reasons.

1. Surgical treatment will not improve vision; the optic nerve and meningeal tumor share a common blood supply. In our experience, attempts to completely separate tumor from optic nerve or chiasm have led to serious visual impairment. No reports of successful removal of a perioptic meningioma can be found in the medical literature.
2. In planning therapy, the slow growth rate of these tumors, illustrated especially by case 3, should be a major factor for consideration.

John T. Fisher, MD, G. W. Taggart, MD, and Robert L. Shindler, MD, referred the patients.

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Hemorrhages With Optic Nerve Drusen

A Differentiation From Early Papilledema

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• The distinction between early papilledema and drusen of the optic disk may be made more difficult by the presence of hemorrhages. We report five patients with drusen of the optic disk and associated hemorrhages. The distinguishing characteristics of both conditions are described.

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Drusen of the optic disk are deposits of hyaline-like material that may be buried or exposed. These excrescences cause a characteristic elevation of the optic disk. Differentiation between drusen and papilledema has been widely discussed in the neurologic and ophthalmologic literature for many years.[1-5] The association of elevated disks and hemorrhages has ordinarily made the neurologist consider papilledema rather than drusen. Only comparatively recently have reports associating hemorrhages and optic disk drusen appeared, and to our knowledge all have been in the ophthalmic literature.[6-13]

This report emphasizes the difference between papilledema and optic nerve drusen with hemorrhages, and presents five cases of the latter condition.

REPORT OF CASES

CASE 1.—A 14-year-old girl appeared to have unilateral left disk edema. One year before, the left disk was noted to have blurred margins. She was asymptomatic at this time. Pertinent physical findings were confined to the eyes. Visual acuity was 6/6 in each eye, there was no deafferented pupil, and the visual field examination was normal. Both optic disks were elevated, and had blurred, irregular margins consistent in appearance with buried drusen. There was no central cup in either eye. The left optic disk had a subretinal, arcuate circumpapillary hemorrhage. Spontaneous venous pulsation was not present in either eye. Lumbar puncture was performed on two occasions with normal opening pressures.

CASE 2.—A 12-year-old boy appeared to have unilateral disk edema of the right eye. He was completely asymptomatic. Pertinent physical findings were confined to the eyes. Visual acuity was 6/6 in each eye. There was no deafferented pupil. Visual field examination revealed slight enlargement of the blind spot in the affected eye. The left disk was normal, with a small central cup and spontaneous venous pulsations. The right disk was elevated, had blurred margins, and had no central cup. A small subretinal hemorrhage was present at the 12 o'clock position on the right disk margin (Fig 1). Spontaneous venous pulsation was not present. The remainder of the ophthalmologic examination was normal. Fluorescein angiography confirmed the presence of optic disk drusen by the demonstration of autofluorescence in the

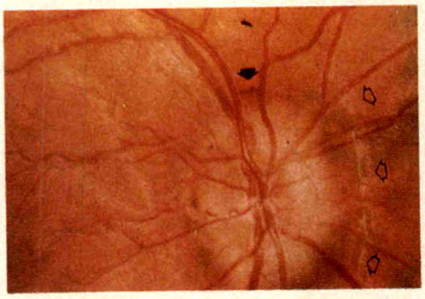


Fig 1.—Case 2. Right optic disk. Note blurred margins and absence of central cup; arcuate, circumpapillary, subretinal hemorrhage (closed arrow); areas of hyperpigmentation at disk; crescentic light reflex off inner surface of retina, nasal to disk (open arrows); and highlighting of light reflexes from retinal vessels and nerve fiber layer.

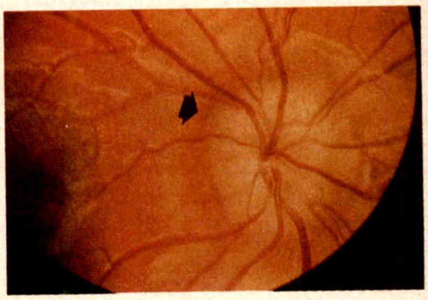


Fig 2.—Case 4. Right eye, 1972. Note optic disk with blurred, irregular margins and absent central cup; subretinal hemorrhage (arrow); and glistening light reflexes on prepapillary retinal vessels.

Fig 3.—Case 4. Right eye, 1974. Note small, flame-shaped hemorrhage (closed arrow).

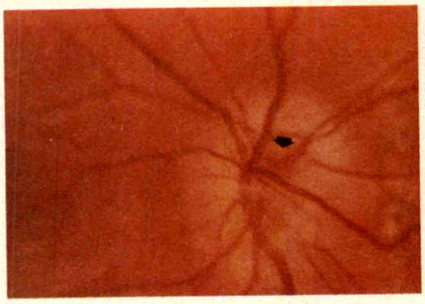
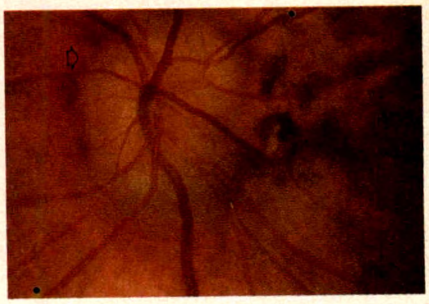


Fig 4.—Case 4. Right eye, 1975. Note resolution of flame-shaped hemorrhage and persistent pigmented lesion at site of previous (1972) subretinal hemorrhage (open arrow).



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preinjection phases and late focal fluorescein staining. Two months later, the peripapillary hemorrhage had resolved.

CASE 3.—A 16-year-old boy was examined because of the appearance of his left optic disk. He was asymptomatic. Ocular examination revealed a visual acuity of 6/5 bilaterally, normal visual fields, and pupillary reflexes. The right disk appeared normal, with a small optic cup. The left disk was elevated and blurred at the margins, with no central cup. The appearance was characteristic of buried disk drusen. A small subretinal hemorrhage was present on the left disk margin. Spontaneous venous pulsations were present in both eyes. Examination of his sister's eyes revealed bilateral drusen.

CASE 4.—A 12-year-old boy had a flame-shaped hemorrhage on the right optic disk. Three years before (1972), blurring of the left disk margin with a contiguous area of chorioretinal degeneration led to the diagnosis of optic neuritis, or possibly, histoplasmosis (Fig 2). No cause for this lesion was found. During a routine follow-up examination, a splinter hemorrhage of the left optic disk was noted. Visual acuity was 6/6 bilaterally, visual fields were normal, and there was no afferent pupillary defect. On fundus examination, both eyes revealed elevated, yellowish-pink optic disks with no central cups, consistent with the appearance of buried drusen. In the left eye, there were multiple pigmentary lesions. The right eye showed a small flame-shaped hemorrhage on the optic disk (Fig 3). There were also multiple small areas of hyperpigmentation on the retina surrounding the optic disk. Review of photographs taken in 1972 (Fig 2) revealed a small subretinal hemorrhage at the 10 o'clock position on the disk margin. This corresponds exactly to a small pigmentary lesion seen in the photographs taken in 1974. Examination five months later showed resolution of hemorrhage and persistence of the pigmentary changes (Fig 4).

CASE 5.—This 12-year-old boy originally had decreased vision in his left eye of an undetermined period of time, headaches, and "papilledema." He underwent extensive neurological and neurosurgical studies, including a suboccipital craniotomy, without definitive diagnosis. Examination three months following surgery revealed a best corrected visual acuity of 6/6 in the right eye and 6/60 in the left eye, with a deafferented left pupil. Fundus examination showed bilateral elevation of the optic disks with exposed drusen. A serous retinal detachment, together with subretinal hemorrhage involving the macular region, was seen in the left eye. The macular lesion accounted for poor vision in this eye.

Comparison of Early Papilledema and Optic Disk Drusen

	Drusen	Early Disk Edema
Symptomatology	Incidental finding Visual disturbances due to: (1) vitreous hemorrhages,[10] (2) field loss,[5,23] or (3) macular dysfunction from subretinal hemorrhage or serous detachment[11,12] Occasional transient visual obscurations[5]	Headaches and transient visual obscurations Vision is unaffected
Family history	Irregular dominant inheritance[5] (examine siblings and parents of patient 3)	Rare familial occurrence of pseudotumor cerebri[24,25]
Associated conditions	Angioid streaks[26] Retinitis pigmentosa[5]	Increased intracranial pressure from any cause
Race	Mostly white (only one report affecting a black[10,27])	Any race
Age at onset	Definite, age-related progression from "buried" to "exposed" drusen Hemorrhages are seen in early teens to early adulthood in most reported cases,[6-13] but may be seen at any age	Any age
Cup	Small or absent[28] (patients 1 through 4)	Preserved
Elevation	Obviously elevated with a tendency for the center of disk to be the highest point of elevation[28]	Minimally elevated, if at all
Margins	Irregular or "lumpy-bumpy" appearance	Smooth and regular margin Indistinct superiorly and inferiorly
Color	Pink to yellowish-pink with variable bright lemon-yellow excrescences	Hyperemic
Nerve fiber layer	Glistening with frequent circumpapillary "halo" of feathery light reflections[15,19]	Dulling of peripapillary nerve fiber layer light reflexes[19]
Vessels	Situated in the center of the disk Frequently anomalous with trifurcations[15,22] Spontaneous venous pulsations usually present Normal glistening vessel light reflexes[28,29]	"Normal" distribution of vessels Absent venous pulsations with full veins Dulling of blood vessel light reflexes[29]
Hemorrhages	Usually single Types: (1) prepapillary "splinter," (2) prepapillary "massive," (3) peripapillary pigmentary changes reported following subretinal hemorrhages (Fig 4)[10,19]	Same types, but multiple splinter hemorrhages in the nerve fiber layer are most common Subretinal hemorrhages are rare in early papilledema and should strongly suggest drusen
Fluorescein angiography	"Autofluorescence" and late focal fluorescence[20-22]	Early fluorescein leakage and late fluorescence[15,20]

COMMENT

Reese[6] in 1940 reported on a 12-year-old boy with prepapillary hemorrhage and drusen; Gallais[7] noted a prepapillary hemorrhage in an 11-year-old girl with drusen of the optic disk; and Bregeat[8] reported single linear hemorrhages in two individuals with optic disk drusen. Lorentzen,[5] however, found no hemorrhages in his series of 70 individuals with optic disk drusen, and considered their association rare. Otradovec and Vladykova,[9] and Sanders et al[10] more recently, have emphasized this association. Sanders et al[10] divided these hemorrhages into the following three groups: (1) small, superficial hemorrhages on the optic disk (these were transient and clinically insignificant, as in case 4 of this series); (2) large hemorrhages on the optic disk, extending into the vitreous humor; (3) deep peripapillary hemorrhages extending from the optic disk under the surrounding retina. Two of their patients had superficial disk hemorrhages, and six had peripapillary hemorrhages. Of these six patients, four were noted to have peripapillary pigmentary changes at the site of the resolved hemorrhage. Similar pigmentary changes were seen in our patients 2, 4, and 5.

Henkind et al[11] and Wise et al[12] reported on eight patients with subretinal peripapillary hemorrhage, emphasizing the visual complications that followed, and Broderick[13] recently reviewed the problem of hemorrhagic complications of drusen, adding two further examples. We have described five patients, ranging in age from 12 to 16 years, in whom the diagnosis of optic disk drusen was made on examination of the optic disks. In each patient, papilledema had been considered, and in one instance this diagnosis resulted in an exploratory craniotomy despite normal neuroradiologic studies.

In most patients, the forms of papilledema, characterized as acute, established, and atropic,[14,15] are sufficiently distinctive to prevent confusion with optic disk drusen. Acute papilledema, with hemorrhages, exudates, and dilated nonpulsatile veins, should not be difficult to differentiate from drusen. In established papilledema, the distinguishing features are multiple dilated capillaries; tortuous, fat, nonpulsatile veins; and opticociliary collateral venous channels. Some confusion may arise in late stages of papilledema, where multiple refractile bodies may appear. These refractile "pseudodrusen" are situated superficially in the substance of the optic disk.[16] They are usually seen at the margins of the disk, and probably represent degenerated axons.[17] There may be associated nerve fiber layer defects or "gutters."[17,18] The flat, white disk of chronic atrophic papilledema[14] bears no resemblance to the elevated disks of optic nerve drusen. It is in early papilledema where doubt and indecision regarding diagnosis may arise. The Table gives the distinguishing features of these conditions. All the physical findings and features tabulated above may be easily visualized using a direct ophthalmoscope with a bright source of illumination and a red-free filter. Pupillary dilatation with mydriatics will make the examination considerably easier to perform. Other family members should always be examined when drusen of the optic disk are suspected. Fluorescein angiography, although not foolproof,[19] is frequently helpful.[20-22]

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Progressive Spastic Paraparesis and Adrenal Insufficiency

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• A 10-year-old boy with progressive paraparesis, personality change, and seizures had laboratory evidence of adrenal insufficiency. Pathologic study showed cerebral edema, but no loss of myelin. Notable pathologic changes were limited to the spinal cord, where the corticospinal and spinocerebellar tracts were demyelinated. Lipid analysis of the brain was normal apart from the finding that galactocerebroside contained a higher proportion than normal of α-hydroxy fatty acids. We suggest that this case represents a distinct disease, differing importantly from adrenoleukodystrophy. The underlying defect appears to be in the early enzymatic pathway before cholesterol synthesis, although it is also possible that the defect is at the cell membrane.

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The association of adrenal insufficiency with diffuse cerebral sclerosis, currently termed adrenoleukodystrophy, has been recognized since 1923.[1,2] The association of adrenal insufficiency with spastic paraplegia has been recognized less frequently. In 1955, Harris-Jones and Nixon[3] reported two brothers with this combination. In 1957, Hewitt[4] reported Addison disease in two sisters, one of whom had spastic legs. In 1960, Penman[5] reported a woman with this combination. Pathologic examinations were not performed in these cases.

In this article, we report the history, adrenal function studies, and autopsy findings in a 10-year-old boy with progressive spastic paraparesis in association with laboratory findings of adrenal insufficiency.

REPORT OF A CASE

The patient was a product of a normal pregnancy and delivery and was the third of four children born to parents who were first cousins. His older brother and his sister both had Klippel-Feil and Sprengel deformities, but no neurologic signs. His younger brother was healthy. There was no other family history of neurologic or psychiatric disease.

The patient's early developmental milestones were normal. He was in good health until the age of 9, when insidiously progressive gait disturbance and personality changes appeared. At age 9½ years, a myelogram was normal, but during this procedure, the child had his first seizure.

On examination at 10 years of age, he was an alert, healthy-appearing boy. His height, weight, and head circumference were at the 25th percentile. Results of a general physical examination were normal. His skin appeared normal. His cranial nerves tested normally, although the jaw jerk was brisk and a snout reflex was present. Strength, tone, and deep tendon reflexes were normal in his arms. In his legs, strength was decreased, tone was increased, and deep tendon reflexes were exaggerated. Abdominal reflexes were absent and the plantar responses were extensor bilaterally. His gait was wide-based and unsteady. Mild dysmetria was present on finger-to-nose testing and was more notable on heel-to-shin testing. The Romberg test gave negative results. Sensory testing was normal. Although psychological testing was only approximate, it showed low-normal intellectual function with performance scores being somewhat lower than verbal scores.

Results of the usual laboratory and radiologic studies were normal, as were the electroencephalogram, brain scan, cerebral angiogram, and cerebrospinal fluid analysis. The motor nerve conduction velocities were slightly slow, measuring 46 meters/sec in the left median, 38 and 37 meters/sec in the left and right peroneal, and 37 and 35 meters/sec in the left and right posterior tibial nerves. The only abnormality noted on the needle muscle examination was fibrillations in the extensor digitorum brevis muscles bilaterally.

Adrenal function studies, which were performed while the patient was receiving mephobarbital (50 mg twice daily), were normal at rest. Blood cortisol levels at 8 AM were 8μg, 14μg, and 15μg/100 ml. Urinary 17-hydroxycorticoid levels were 1.6 and 2.1 mg/sq m/24 hr and urinary 17-ketosteroid values were 0.9 and 1.2 mg/24 hr. Response to adrenocorticotropic hormone (ACTH) stimulation was abnormal. The ACTH gel was administered intramuscularly at 20 units every 12 hours for three consecutive days. Blood cortisol levels at 8 AM on the second, third, and fourth days failed to increase (17μg, 9μg, and 8μg/100 ml). Similarly, there was no increase in the urinary 17-ketosteroid levels, which measured 0.7, 1.1, and 0.6 mg/24 hr, and little increase in the urinary 17-hydroxycorticoid values, which measured 2.7, 3.4, and 4.0 mg/sq m/24 hr. Urinary aldosterone levels were normal, measuring 2.1μg/day on a normal diet and 15.6μg/day on the fourth day of a 0.5-gm salt diet. Serum electrolyte levels remained normal when salt intake was restricted. Blood testosterone level (47μg/100 ml) was normal for a prepubertal boy. All the above values were obtained with previously described methods.[6-10] Urine specimens were analyzed before and after ACTH stimulation to seek evidence for accumulation of precursors in the synthetic pathways of cortisol from cholesterol. There was no evidence of accumulation of any 3-β-hydroxy Δ^5 steroidal compounds by the Oertel reaction for C-21 and C-17

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Glycosphingolipids Isolated From Gray and White Matter

Glycosphingolipid	Gray Matter*		White Matter*	
	Control	Patient	Control	Patient
Galactocerebrodise with normal fatty acid	59.0	35.8	402	139.2
Galactocerebroside with α-hydroxy fatty acid	67.0	128.0	460	479.0
Lactosylceramide	2.0	6.2	0.3	16.3
Sulfatide	47.0	58.0	195.0	235.0

*Values are expressed as μmoles/100 gm fresh weight.

steroids[11] or by the Allen blue reaction for C-17 steroids.[12] Pregnanetriol and tetrahydro S were not found in notable quantities.

Results of adrenal function studies performed on the patient's brothers were normal. The 7-year-old brother's pre-ACTH urinary 17-hydroxycorticoid levels measured 1.4 and 2.0 mg/sq m/24 hr and rose to 16.6 mg/sq m/24 hr on the third day of ACTH stimulation. The 14-year-old brother's pre-ACTH urinary 17-hydroxycorticoid levels measured 3.5 and 4.2 mg/sq m/24 hr and rose to 23.1 mg/sq m/24 hr. Urinary 17-ketosteroid levels rose from 0.8 to 2.9 mg/24 hr on ACTH stimulation in the 7-year-old and from 7.5 to 18.5 mg/24 hr in the 14-year-old.

The patient was discharged on a regimen of mephobarbital therapy. During the next four months, unsteadiness increased, minor motor seizures appeared, and behavior deteriorated. At 10½ years of age, a sural nerve biopsy specimen was normal. One month later, seizures became intractable. Despite corticosteroid replacement, the child died five days later.

RESULTS

Pathologic Findings

A general autopsy performed three hours after death showed no appreciable pathologic findings. The configuration and total weight (10 gm) of the adrenal glands were normal, and histologic sections showed no abnormalities. The pituitary gland was largely destroyed by a recent anemic infarct that involved two thirds of the anterior lobe and a small portion of the posterior lobe.

The brain weighed 1,320 gm, and, except for changes of antemortem autolysis, brain and spinal cord appeared normal grossly.

Samples taken from the cortex, white matter, caudate nucleus, lentiform nucleus, thalamus, hypothalamus, internal capsule, cerebral peduncle, midbrain, cerebellum, pons, medulla, and various levels of the spinal cord and cauda equina were examined by light microscopy. Paraffin sections (6μ thick) were stained with hematoxylin-eosin, Klüver-Barerra, and Bodian stains. Frozen sections were stained with oil red O.

Advanced antemortem autolysis, edema, and vascular engorgement appeared in all sections of the brain, but extensive samples showed no evidence of demyelination (Fig 1).

Symmetric pallor of the lateral columns was evident from Klüver-Barerra staining throughout the entire length of the spinal cord. The loss of myelin was greatest in the posterior spinocerebellar tract, fanning out into the lateral pyramidal tract (Fig 2). Fiber tracts in other areas of the spinal cord were uninvolved. In addition, there appeared to be slightly fewer anterior horn cells in the thoracic segment with the remaining neurons exhibiting some atrophic changes. There appeared to be fewer cells in the Clarke columns in the lower thoracic segment. A few isolated axonal spheroids were seen in the anterior gray horns. The spinal nerve roots showed a mild proliferation of Schwann cells. Sections from the cauda equina had several segments containing ballooned axons.

Samples from the adrenal gland, brain, spinal cord, and sciatic nerve were examined by electron microscopy. The adrenal cortical cells showed no abnormal inclusions such as those described by Powers and Schaumburg.[13] Examination of the brain and spinal cord was unsatisfactory because of autolysis. There was an increase in neurofilaments in the sciatic nerves, yet no abnormal inclusions were found in the Schwann cells.

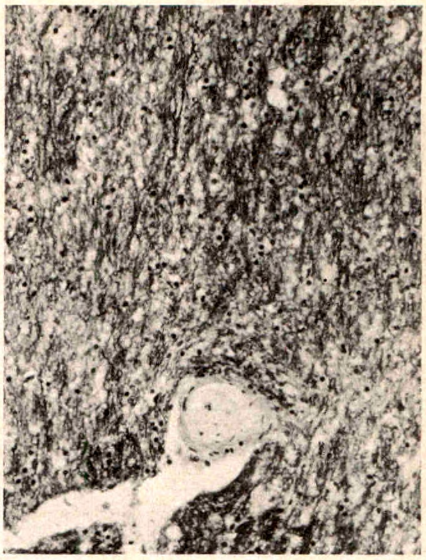

Fig 1.—Cerebral white matter showing well-stained myelinated nerve fibers separated by edema fluid. Cells are normal and blood vessels are unaltered (Klüver-Barerra, ×160).

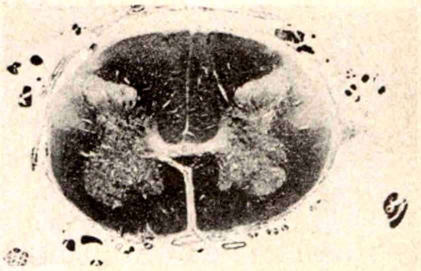

Fig 2.—Thoracic spinal cord showing symmetric pallor of myelinated nerve fibers of lateral columns (Klüver-Barerra, ×20).

Biochemical Findings

At autopsy, samples of gray and white matter from the occipital lobes were immediately frozen in liquid nitrogen and kept frozen at −40 C until they were analyzed. Lipid analysis was performed with methods described previously.[14] The total amount of brain lipid and the composition (proportions of cholesterol, phospholipid, sulfatide, and ganglioside) were normal. Cholesterol esters were low, as in normal controls. Free fatty acid levels were higher than in controls, especially palmitate, stearate, oleate, and linoleate. Total galactocerebroside and sulfatide levels were normal in gray matter and slightly low in white matter. However, there was much more galactocerebroside with α-hydroxy fatty acids than galactocerebroside with normal fatty acids (Table). In gray matter, the ratio was about 4:1 and in white matter the ratio was about 3.5:1; normal values are about 1.5:1. In addition, lactosylceramide levels were high in both gray matter and white matter.

COMMENT

The association of adrenal insufficiency with diffuse cerebral sclerosis was thought to be coincidental when the first few cases were reported.[1,15,16] At present, this unusual combination is thought to be a distinct disease, referred to as adrenoleukodystrophy (ALD).[2] Similarly, the less frequently reported association of adrenal insufficiency with progressive spastic paraparesis seems to be a distinct disease. It differs from ALD in its clinical presentation, mode of inheritance, and pathologic findings.

Patients with ALD have initial symptoms in late childhood of insidious dementia and cortical blindness. The disease is transmitted as a sex-linked recessive disorder.[17] Pathologically, severe symmetric demyelination is seen in the occipital, parietal, and temporal lobes[2]; the adrenal glands are grossly atrophic with ballooned cortical cells containing intracytoplasmic lamellae.[13] In contrast, patients with hereditary spastic paraplegia show signs at various ages of gait disturbance. Various modes of inheritance have been described; the most rapidly progressive course occurs in patients with autosomal recessive inheritance patterns.[18] Our patient's parents were first cousins, which suggests an autosomal recessive disease, and the course, which was rapid, lasted 18 months. Pathologically, our patient's white matter was edematous, but myelin was well preserved. The adrenal glands appeared normal and intracytoplasmic lamellae could not be identified. Appreciable pathologic changes were limited to the spinal cord, where the corticospinal and spinocerebellar tracts were demyelinated. These changes are similar to the changes described in familial spastic paraplegia.[19]

However, results of brain lipid analyses and adrenal function studies are similar in both diseases. In ALD, lipid analysis of the brain is nearly normal, despite almost total destruction of the architecture of the white matter[20] The only abnormality is a slight decrease in the total concentration of cerebroside with a higher proportion of cerebroside containing short-chain fatty acids. Similarly, in our patient, brain lipid analysis was nearly normal, and the main abnormality was in the composition of the fatty acids of cerebroside—namely, a higher proportion of galactocerebroside containing α-hydroxy fatty acids, especially cerebronic acid.

In our patient, as in most patients with ALD, there was no clinical evidence of adrenal insufficiency. As with ALD patients, there was no response to ACTH stimulation. The finding of adrenal unresponsiveness along with pathologic changes compatible with spastic paraparesis suggests that this combination might be detected more frequently if adrenal function studies were performed on patients with progressive spastic paraparesis even when there was no overt evidence of adrenal failure.

Despite the unresponsiveness of the adrenal glands to ACTH stimulation, there was no accumulation of 3-β-hydroxy Δ^5 steroidal compounds, pregnanetriol, or tetrahydro S in our patient. The same has been true for our ALD patients (unpublished data). Thus, there is no evidence that a block in steroid synthetic pathways exists at the level of conversion to Δ^5-pregnenolone or subsequent enzymatic conversions. The defect, if one exists, must be placed further back in the synthetic pathway, where cholesterol or cholesterol precursors become available for the actions of the specific enzymes. Although this seems to be the most likely defect, other possibilities exist. Because ACTH is thought to activate adenyl cyclase, thus producing high-energy phosphorylated compounds, failure of ACTH responsiveness could occur as early as the entry of ACTH through the cell membrane.

Despite the similar results of brain lipid analyses and adrenal function studies in patients with ALD and in our patient, we believe that the clinical, genetic, and pathologic differences indicate that the appearance of adrenal insufficiency with progressive spastic paraparesis is a distinct disease.

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Bilateral Sixth Nerve Palsy

Analysis of 125 Cases

James R. Keane, MD

• Bilateral abducens nerve pareses were nearly as common as unilateral cases in an inpatient setting (125:143). Cerebrospinal fluid abnormalities were more frequent among the bilateral cases, but generally the same causes produced unilateral and bilateral sixth nerve palsy. The relative ease of diagnosis was in contrast with the large number of undiagnosed or "vascular" cases in previous studies of outpatients. The degree of lateral rectus limitation proved to be of limited help in suggesting the cause or predicting recovery of oculomotor function. The etiology was of some prognostic value, with universal recovery of pressure palsies and rare improvement with tumor involvement. Myasthenia, orbital muscle entrapment, convergence spasm, divergence palsy, and pretectal pseudoconvergence entered into the differential diagnosis, but were only occasionally difficult to exclude.

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Most clinical reviews of abducens nerve palsy concern patients presenting to ophthalmologists.[1-4] In the group of more seriously ill patients seen in a neurology inpatient setting, the differential diagnosis is substantially different and bilateral involvement of the sixth nerve is more common.

SUBJECTS AND METHODS

One hundred twenty-five consecutive personally examined inpatients with bilateral abducens palsy over a 5½-year period are analyzed and compared to 143 patients with unilateral sixth nerve involvement seen concurrently.

Most patients exhibited gross limitation of abduction in each eye; minor degrees of limitation were confirmed by the presence of severe slowing of abduction and by the demonstration of consistently incomplete abduction on red-glass or Lancaster diplopia testing. Oculocephalic and caloric stimulation of eye movements were utilized in an occasional stuporous patient to confirm the presence of abduction weakness.

Patients with congenital abducens paresis were included only if they had an oculomotor diagnostic problem in the absence of history. Where limitation of abduction due to mechanical restriction in the orbit was a possibility, a forced duction test was performed to evaluate passive motion of the globe. An edrophonium test was administered whenever myasthenia gravis was a consideration.

Rarely, the presentation of bilateral abducens weakness may be as acute concomitant esotropia.[5] Some patients with acute ocular motor pareses (particularly trochlear nerve palsies) initially exhibit a circumscribed field of diplopia that shifts with time toward a pattern of concomitant diplopia with separation of images in other fields of gaze. A rare patient with slowly progressive sixth nerve compromise secondary to increased intracranial pressure could theoretically develop a shift toward comitance before diplopia becomes manifest and appear as comitant esotropia. Such an occurrence must be rare since only one adult with acute concomitant diplopia (and normal intracranial pressure) was seen during the period of this study and was not included because of the diagnostic confusion with a supranuclear "divergence palsy."

Voluntary ("hysterical") convergence spasm was commonly mistaken for bilateral sixth nerve palsy when the patient was admitted to the neurology service, but a brief period of observation revealed the accompanying pupillary miosis and the inconsistency of the "neurologic" findings.

The esotropia that occurs frequently with pretectal lesions probably represents uninhibited oculomotor activity predominating in the medial rectus muscles,[6,7] but is frequently misdiagnosed as "increased convergence" or bilateral abducens weakness. The detection of superimposed, true partial abducens palsy accompanying a pretectal syndrome may require ocular electromyography.

Analysis by etiology produces certain inequities: patients with the Wernicke-Korsakoff syndrome frequently improve before consultation is requested and this diagnosis is undoubtedly underrepresented here. Pontine tegmental involvement of the sixth nerve may be obscured by complex horizontal eye movement difficulties. Conversely, the category of demyelinating disease includes probable as well as verified cases of multiple sclerosis, in addition to patients diagnosed as having postinfectious encephalopathy, and is undoubtedly too generous.

RESULTS

Seventy-two (58%) of the patients were male—about the same proportion as the neurology service admissions in general. The patients were widely distributed in age, but surprisingly, only one was over 70 years of age.

The precise location of sixth nerve involvement was rarely evident, but in three fourths (93) of the patients, the damage was probably peripheral rather than intrapontine. Many patients exhibited other neurologic signs and

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Table 1.—Etiologic Factors of Bilateral and Unilateral Abducens Pareses

	Bilateral Cases	Unilateral Cases
Tumor		
Local	16	14
Distant	12	12
Demyelinating disease	17	13
Subarachnoid hemorrhage	16	10
Infection	12	9
Trauma	11	19
Guillain-Barré syndrome	9	3
Nonlocalized increased intracranial pressure	8	5
Wernicke-Korsakoff syndrome	7	1
Brain stem infarction	6	31
Congenital	3	2
Supratentorial stroke	3	1
Recurrent cranial neuropathy	1	3
Vasculitis	1	4
Aneurysm, unruptured	...	2
Arteriovenous malformation, brain stem	...	2
Diabetes	...	3
Other	...	3
Unknown	3	6
Total	**125**	**143**

Table 2.—Tumors Producing Bilateral Abducens Palsy

Direct Involvement Probable	**No. of Cases**
Cavernous sinus localization	
Nasopharyngeal carcinoma	3
Chromophobe adenoma (pituitary apoplexy)	3
Craniopharyngioma	1
Cavernous sinus metastasis	1
Posterior fossa localization	
Pontine glioma	2
Cerebellopontine angle epidermoid cyst	2
Cerebellopontine angle meningioma	1
Middle and posterior fossa meningioma	1
Meningeal gliomatosis	1
Meningeal myeloma	1
Total	**16**
Indirect involvement probable	
Supratentorial glioma	4
Cerebral metastases	3
Cerebellar metastasis	1
Cerebellar astrocytoma	2
Cerebellar "cyst"	1
Medulloblastoma	1
Total	**12**

symptoms, and one quarter (31) had involvement of other cranial nerves.

The etiologic agent was usually apparent within several weeks of the onset of bilateral sixth nerve impairment. A reasonably secure, general diagnosis was made in all patients, except two with chronic palsies and limited histories, and one patient with acute self-limited palsies in association with a peripheral neuropathy and normal cerebrospinal fluid (CSF).

In one third (44) of the patients, CSF abnormalities including hemorrhage, inflammation, and increased pressure were the immediate cause of the abducens palsy. The most common, single etiologic agent among a varied list of causes (Table 1) was tumor with 28 cases represented. Sixteen tumors were in a position to directly involve the nerves, whereas the remaining 12 presumably acted through an increase in pressure or distortion of intracranial contents. No single type of tumor predominated, but the site of direct involvement was more commonly in the cavernous sinus region (eight cases) than in the posterior fossa (six cases), with two cases associated with widespread meningeal tumor (Table 2). Diffuse meningitis (two bacterial, one tuberculous, one syphilitic, and five cases probable viral cause) was the usual diagnosis in the infection category, but three patients had primary parameningeal bacterial lesions.

Although direct tumor involvement and trauma tended to cause complete abducens paralysis, the degree of lateral rectus limitation was of little help in predicting the etiology. Follow-up was incomplete in many patients, but the degree of lateral rectus limitation appeared, at best, to be of slight prognostic value. One month after onset, complete recovery had occurred in two thirds of the patients followed up who had had mild or moderate limitation of lateral rectus movement and in one half of those with total palsies.

The etiology provided a somewhat better clue toward outcome: relief of increased intracranial pressure almost always resulted in prompt resolution of pressure palsies, whereas the only instances of clearing with direct tumor involvement occurred in two patients following surgery for pituitary apoplexy. Complete recovery occurred in all cases of Wernicke-Korsakoff and Guillain-Barré syndromes. The outcome was less predictable for the inflammatory and traumatic cases.

The group of patients with *unilateral* abducens involvement included more people over age 70 years and slightly fewer under age 20 years. Cerebrospinal fluid abnormalities were a common cause of both bilateral and unilateral sixth palsies, but more frequently produced bilateral involvement (Table 1). Brain stem infarcts were more likely to appear as unilateral sixth nerve impairment; small-vessel disease associated with diabetes and vasculitis rarely produced bilateral simultaneous abducens palsies. Sixth nerve involvement was more often bilateral in the Wernicke-Korsakoff and Guillain-Barré syndromes. The etiology of the unilateral cases was frequently obscure initially and became evident only after months of follow-up, whereas the cause of bilateral sixth nerve palsy was usually determined during the initial hospitalization.

COMMENT

By far the largest series of patients with abducens palsy is included in Rucker's analyses[1,2] of 2,000 consecutive cases of third, fourth, and sixth nerve paralysis from the Mayo Clinic. Of his 2,000 patients, 1,152 exhibited sixth nerve involvement, and in one fourth (289 of 1,152), the etiology was not determined. Bilateral sixth nerve involvement was not considered separately in this series.

There were 29 bilateral examples in a series of 133 acquired sixth-nerve pareses in childhood in a separate study from the Mayo Clinic.[8] Eleven bilateral cases were secondary to tumor, five were traumatic, seven inflammatory, one vascular, four miscellaneous, and only one of undetermined cause.

Bilateral involvement occurred in 29 of 158 cases of sixth-nerve palsy in a review that emphasized corrective eye surgery.[4] As expected, the incidence of traumatic cases (14 bilateral) was high and the number with tumor (three), multiple sclerosis (one), and vascular cause (one) relatively low.

Only five bilateral cases were reported in the Wills Eye Hospital study of 104 patients with abducens pareses in which patients with papilledema and other cranial nerve deficits were excluded.[3] The etiologic agent was uncertain in 45% of this group (including a vascular category), and in 15%, the presumptive cause was diabetes. Causes of bilateral palsies included one example each of diabetes, multiple sclerosis, syphilis, sinusitis, and undetermined.

The relative ease of diagnosis in the present series appears to relate to both the bilateralness of abducens weakness and the seriousness of illness. Small-vessel occlusive disease is unlikely to produce simultaneous infarction of both abducens nerves; many of the patients with "hypertensive" or "unknown" diagnoses in previous series of unilateral sixth-nerve involvement undoubtedly suffered from nerve-trunk ischemia. However, the paucity of "microvascular" *unilateral* sixth nerve palsy cases in our population seems only partially explained by a bias toward severe disease; it is possible that some of the reported "vascular" abducens palsies may represent minor episodes of subarachnoid hemorrhage or brain stem infarction.

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Lowering Brain Phenylalanine Levels by Giving Other Large Neutral Amino Acids

A New Experimental Therapeutic Approach to Phenylketonuria

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• Hepatic phenylalanine hydroxylase activity was inhibited in F344 rat pups by injection with parachlorophenylalanine on days 7, 8, and 9 after birth. On day 10, animals were divided into control and experimental groups. Controls received an injection of phenylalanine, with the characteristic phenylketonuria (PKU) changes of elevated phenylalanine but normal tyrosine levels. The experimental group received a similar injection of phenylalanine but in addition received either a single amino acid or a combination of amino acids from the large neutral amino acids (LNAA) group. The LNAA group of amino acids—phenylalanine, tyrosine, tryptophan, leucine, isoleucine, and valine—compete with each other for entry into brain by a common transport mechanism. Compared with controls, the experimental group had lower phenylalanine levels in brain, but no change in serum levels, giving a lower brain-serum phenylalanine ratio. Increasing the serum concentrations of amino acids competitive with phenylalanine for transport across the blood brain barrier might form an alternative approach to effective dietary treatment of PKU.

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Recent work has clarified biochemical correlates of neurologic dysfunction in phenylketonuria (PKU). Guroff and Udenfriend[1] suggested that mental retardation in the aminoacidurias might result from overloading of a common mechanism for transport of large neutral amino acids (LNAA) across the blood brain barrier. Oldendorf[2,3] and other workers[4-6] have demonstrated that these LNAA traverse the blood brain barrier via a saturable transport mechanism and have also shown that an increased serum phenylalanine level impedes transport of these related amino acids. McKean and co-workers[4] have verified intracerebral deficiencies of threonine, valine, methionine, isoleucine, leucine, histidine, tryptophan, and tyrosine in adult and fetal rat brain as a result of induced hyperphenylalaninemia. This results in depression of protein and lipoprotein synthesis by brain both in vivo[7,8] and in vitro.[9-11] The relative contributions to the brain damage of the elevated phenylalanine level and the possibly critical lowering of the other LNAA sharing the same transport system with phenylalanine have not been determined.

Current therapy in PKU is directed toward restriction of dietary phenylalanine. In this report, we examine the feasibility of another approach to PKU treatment: to lower the excess cerebral phenylalanine levels and to increase the deficient levels of cerebral LNAA by administering either individual amino acids or combinations of amino acids from the LNAA group (other than phenylalanine), which compete with phenylalanine for transport across the blood brain barrier.

SUBJECTS AND METHODS

F344 rats were received in the laboratory on day 17 of gestation. Animals were individually housed and received food pellets

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and water ad lib. Litters were undisturbed after birth. All pups were injected subcutaneously on days 7, 8, and 9 after birth with 60 mg/kg of body weight of parachlorophenylalanine in 0.015M solution, in order to inhibit hepatic phenylalanine hydroxylase activity. Parachlorophenylalanine was prepared as reported previously.[12] These animals with lowered phenylalanine hydroxylase activity were then divided into control (PKU) and experimental (PKU plus competitor) groups for treatment on day 10. On day 10, animals designated "control group" were injected with 1μmol phenylalanine per gram of body weight (20μl/gm of body weight of a 0.05M solution of phenylalanine), a regimen shown to produce a PKU-like condition of elevated phenylalanine levels but normal tyrosine levels. Littermate experimental animals received 1μmol of phenylalanine per gram of body weight, as above, plus the treatment of either 5μmol/gm of body weight of a single competitive amino acid from the LNAA group, or 1μmol/gm of body weight each of the combination of isoleucine, leucine, tryptophan, tyrosine, and valine (LNAA mixture). Control and experimental animals received the same injection volume in all cases.

On day 10, samples of blood and brain were obtained in littermates immediately prior to injections in order to determine baseline phenylalanine levels in these tissues. Samples of blood and brain were then obtained one hour after injection of either phenylalanine alone (control group) or phenylalanine plus competing amino acid(s) (experimental group). At least three animals were used for each determination. Animals for any individual experiment came from a single litter. Blood and brain phenylalanine levels were determined at 30 and 90 minutes after injection, as well as at 60 minutes, for the trial comparing phenylalanine alone vs phenylalanine plus the mixture of five LNAA.

Animals were anesthetized with pentobarbital sodium, and blood was collected into a heparinized capillary tube from the subclavian vein. The thorax was opened and the aorta was injected with 3 ml of heparinized saline solution. The brain was then removed, frozen on dry ice, and wrapped in foil. Brain was homogenized in five volumes of 0.36N trichloroacetic acid (TCA) and centrifuged ten minutes at 5,000 rpm. A 50μl sample of plasma was deproteinized with 50μl 0.6N TCA and centrifuged, as previously described. Phenylalanine determinations were performed in duplicate by the method of McCaman and Robins,[13] with phenylalanine standards prepared in 7.5% bovine serum albumin (BSA).

RESULTS

Baseline phenylalanine levels in brain and serum were subtracted from one-hour values and results were expressed as change in phenylalanine level. Animals receiving phenylalanine plus competitor were compared with controls injected with phenylalanine alone. The data are presented in the Table. Brain-serum phenylalanine ratios, therefore, represent the change in brain phenylalanine level divided by the change in serum phenylalanine level from baseline measurements to one hour after injection (Table and Fig 1). *P* values, derived from determination of the relative deviate, indicate the significance of the difference between the means of the experimental and control groups for each competitor.

Administration individually of isoleucine, leucine, threonine, tryptophan, tyrosine (as suspension), and valine each resulted in significant lowering of brain phenylalanine in relation to control animals (Table). The LNAA mixture was similarly effective. In contrast, serum phenylalanine levels were not significantly affected by the injection of competitor amino acid(s) along with the phenylalanine. Therefore, brain-serum phenylalanine ratios declined significantly in animals injected with phenylalanine plus competitor(s). Threonine, which was noted by McKean et al[4] to be decreased in brain by high circulating phenylalanine levels, was also found in this experiment to lower brain phenylalanine levels as compared with controls. This observation suggests that threonine may share some aspects of the LNAA transport system. Glycine, which is transported primarily via a different carrier system,[6] had no significant effect on either serum or brain phenylalanine levels, and therefore served as an active control for the possible nonspecific effect of the conpeting amino acid(s).

A relationship between dose of competing amino acid and degree of phenylalanine exclusion from brain is suggested by the statistically significant additional 30% reduction of the brain phenylalanine level that was achieved by doubling the amount of valine (valine 2×) administered, from 5μmols/gm to 10μmols/gm (Table and Fig 1).

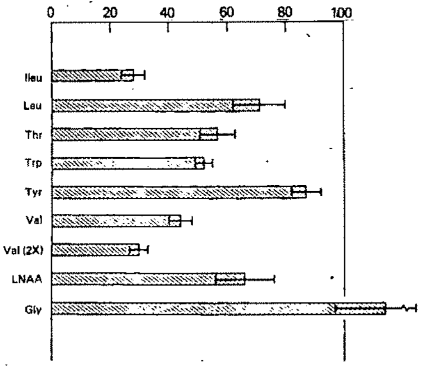
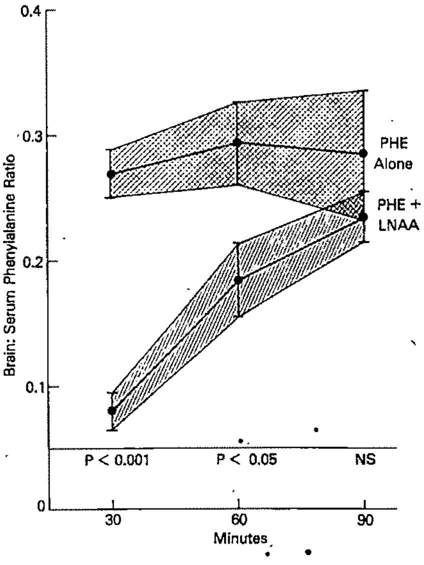


Fig 1.—Ratio of brain-serum phenylalanine levels one hour after injection of phenylalanine plus competitive amino acid(s) as percent of same ratio in control animals injected with phenylalanine alone (see text). Data are from Table. Bars represent standard error of mean. Ileu indicates isoleucine; Leu, leucine; Thr, threonine; Trp, tryptophan; Tyr, tyrosine; Val, valine; Val (2×), double amount of valine; LNAA, large neutral amino acids; Gly, glycine.

Fig 2.—Time course of brain-serum phenylalanine (Phe) ratio after injection of phenylalanine plus large neutral amino acids (LNAA) or phenylalanine alone (see text). Bars represent standard error of mean.



The time course of relative phenylalanine exclusion from brain by the LNAA mixture is shown in Fig 2. Changes in brain and serum phenylalanine levels were determined 30, 60, and 90 minutes after injection of phenylalanine plus LNAA and after

Changes in Serum and Brain Phenylalanine Levels and Changes in Brain-Serum Phenylalanine Ratio*

Injection	No. of Rats	Change in Phenylalanine Level, mg/100 ml†		Ratio of Change in Brain Phenylalanine to Change in Serum Phenylalanine†
		ΔSerum	ΔBrain	
Phenylalanine + isoleucine	4	17.1 ± 1.9‡	1.7 ± .3§	0.10 ± 0.02‖
vs phenylalanine alone	3	21.1 ± 2.7	7.5 ± 2.4	0.36 ± 0.2
Phenylaline + leucine	3	14.2 ± 0.9‡	4.2 ± 0.5‖	0.30 ± 0.04¶
vs phenylalanine alone	3	16.2 ± 2.4	6.8 ± 1.1	0.42 ± 0.6
Phenylalanine + threonine	3	14.9 ± 1.3‡	3.6 ± 0.2‖	0.24 ± 0.01‖
vs phenylalanine alone	3	16.2 ± 2.4	6.8 ± 1.1	0.42 ± 0.6
Phenylalanine + tryptophan	3	14.3 ± 1.6‡	3.75 ± 0.3§	0.26 ± 0.02§
vs phenylalanine alone	3	13.6 ± 1.3	6.6 ± 1.0	0.49 ± 0.04
Phenylalanine + tyrosine	3	10.5 ± 1.3‡	4.7 ± 0.1‖	0.45 ± 0.01§
vs phenylalanine alone	3	10.3 ± 0.6	5.3 ± 0.2	0.52 ± 0.02
Phenylalanine + valine	3	10.4 ± 1.6‡	2.6 ± 0.2§	0.25 ± 0.02§
vs phenylalanine alone	3	8.8 ± 2.0	5.0 ± 0.06	0.57 ± 0.06
Phenylalanine + valine 2×	3	10.7 ± 0.1‡	1.8 ± 0#	0.17 ± 0.01#
vs phenylalanine alone	3	8.8 ± 2.0	5.0 ± 0.6	0.57 ± 0.06
Phenylalanine + large neutral amino acids**	2	13.8 ± 1.0‡	2.6 ± 0.5‖	0.19 ± 0.03‖
vs phenylalanine alone	3	16.1 ± 1.9	4.7 ± 0.6	0.29 ± 0.04
Phenylalanine + glycine	2	14.5 ± 2.3‡	4.7 ± 0.4‡	0.33 ± 0.03‡
vs phenylalanine alone	3	16.1 ± 1.9	4.7 ± 0.5	0.29 ± 0.04

*These changes took place one hour after injection of either phenylalanine plus competitor(s) or phenylalanine alone (see text).

†All values expressed as mean ± SE.

‡$P > .1$.

§$P < .001$ vs control.

‖$P < .05$ vs control.

¶ $P < .1$.

#$P < .001$ vs valine.

**Isoleucine, leucine, tryptophan, tyrosine, valine.

phenylalanine alone. The effect of the LNAA mixture on brain-serum phenylalanine ratio is most marked at 30 minutes and is virtually undetectable 90 minutes after injection.

COMMENT

These experiments do not deal with the effect of hyperphenylalaninemia on organs other than brain. While in utero hyperphenylalaninemia may produce multiple congenital defects, the only organ critically affected by postnatal hyperphenylalaninemia is the rapidly developing and vulnerable brain. Except for eczema that may be persistent, but which otherwise will not disturb normal development, few organs other than brain appear to be seriously affected by elevated plasma phenylalanine levels. Primary effort should be directed toward restoring normal cerebral levels of amino acids.

These data demonstrate that in developing, hyperphenylalaninemic rats, increasing the serum levels of amino acids that are competitive with phenylalanine for transport across the blood brain barrier lowers brain phenylalanine levels and therefore lowers the brain-serum phenylalanine ratio. It would be of great interest and potential clinical relevance to explore the ability of such a regimen, not only to exclude phenylalanine from the brain, but also to correct the existing intracerebral deficiencies of amino acids that are competitive with phenylalanine for transport into brain. This might form the basis for an effective alternative approach to therapy that employs addition of competitive LNAA to the diet rather than subtraction of phenylalanine alone.

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Acute Renal Failure

A Complication of Cerebral Angiography

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• Acute renal failure after cerebral angiography is, to our knowledge, previously undescribed, yet well documented after other forms of angiography and intravenous urography. We will describe four patients with this complication and discuss factors in its pathogenesis.

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Acute renal failure has been reported after intravenous urography and extracerebral angiography.[1-3] This communication documents its occurrence after cerebral angiography, reviews factors that may operate in its pathogenesis, and suggests means of reducing its incidence.

REPORT OF CASES

Case 1.—A 70-year-old hypertensive man collapsed on the day of hospital admission. He had a previous history of left hemiparesis 15 months before admission. There was no knowledge of preexistent renal disease or diabetes mellitus. On initial examination, he was comatose, with a blood pressure of 250/150 mm Hg. Pupils were 3 mm equal and reactive. Doll's eye phenomenon was present. There was bilateral lower extremity spasticity, with hyperreflexia greater on the left. Laboratory studies disclosed the following values: fasting blood glucose, 174 mg/100 ml; blood urea nitrogen (BUN), 22 mg/100 ml; and serum creatinine, 2.0 mg/100 ml. Urinalysis showed specific gravity of 1,010, pH 5.0, albumin (2+), glucose (1+), no

After arteriography, the patient's urinary output fell to 20 ml/hr, and despite administration of normal saline solution, the patient became progressively azotemic, with levels of BUN and serum creatinine increasing to 108 mg/100 ml and 4.5 mg/100 ml, respectively, six days later. There was no response to 120 mg of furosemide given intravenously. On hospital day 8, the patient died. Autopsy showed right hemispheric hemorrhagic infarction and bilateral nephrosclerosis.

Case 2.—A 60-year-old diabetic hypertensive woman had been treated with insulin for 20 years and with oral hypoglycemic agents for six years. She had severe retinopathy and hypertension treated with methyldopa and hydrochlorothiazide. Examination showed a chronically ill woman, with bilateral cataracts and normal cardiopulmonary function. Blood pressure was 186/104 mm Hg. She was sleepy and disoriented, but was aroused by questioning. There was disorientation as to the year and month, but her speech was intact. Cranial nerve examination indicated diabetic retinopathy and reduced visual acuity. She had an ataxic gait and decreased vibration and position sense in both lower extremities.

Laboratory studies disclosed the following values: blood glucose, 380 mg/100 ml; serum sodium, 141 mEq/liter; serum potassium, 4.1 mEq/liter; serum calcium, 9.3 mg/100 ml; BUN, 28 mg/100 ml; and serum creatinine, 2.5 mg/100 ml. Examination of a 24-hour urine sample showed the following values: protein, 1 gm; specific gravity, 1.018; glucose, 1+; two to five WBCs per high power field; zero to two WBCs per

56 mg/100 ml, with the serum creatinine level at 5.2 mg/100 ml. Despite vigorous intravenous administration of fluids, the levels of BUN and serum creatinine continued to rise to 69 mg/100 ml and 7.8 mg/100 ml, respectively, on hospital day 8. Over the next six days, urinary output increased to 4.2 liters/day, with return of creatinine clearance to the prearteriography baseline.

The patient died two weeks later. Autopsy showed generalized arteriosclerosis, with bilaterally small kidneys that had the changes of intercapillary glomerulosclerosis. Renal tubules showed regenerative changes compatible with recent previous injury. There was a patchy interstitial infiltrate of lymphocytes, severe vascular disease in the brain, and a recent infarct in the left cerebral hemisphere.

Case 3.—A 74-year-old diabetic man was admitted for elective repair of fractured os calcis. After unsuccessful attempts at epidural anesthesia, with return of grossly bloody fluid, spinal anesthesia was obtained, and uneventful open repair was accomplished. There was no hypotension. Postoperatively, the patient complained of headache, and 24 hours later he was comatose and febrile.

Because of fluctuating levels of consciousness, a cerebral arteriogram was performed. The procedure was difficult because of tortuous vessels, and a 300-ml dose of diatrizoate meglumine was administered. No abnormalities were seen.

Twelve hours after angiography, urine output fell to 5 ml/hr, and the level of serum creatinine rose from 1.2 to 2.1 mg/100 ml. Findings from urinalysis were normal, except for glycosuria. Levels of serum calcium, electrolytes, and uric acid, and protein electrophoresis were normal. Despite intravenous administration of a large amount of fluid and intravenous administration of 400 mg furosemide, urine output remained low and the level of

[redacted]

Examination showed a blood pressure of 200/100 mm Hg and cardiac enlargement. Distal pedal pulses were absent. Nuerological examination showed distal vibratory sensory loss and absent ankle jerks.

Laboratory studies disclosed the following values: hematocrit reading, 32%; glucose, 130 to 175 mg/100 ml; BUN, 30 mg/100 ml; and serum creatinine, 2.0 mg/100 ml.

A carotid, vertebral, and aortic arch angiogram was performed without incident. Approximately 220 ml of contrast medium was used. On the day after angiography, the patient developed a sinus bradycardia; an examination of serum electrolytes showed the potassium level to be 6.9 mEq/liter. The patient developed oliguria, and the level of serum creatinine increased to a maximum of 4.3 mg/100 ml four days after angiography. She was treated with cation exchange resin and a low-potassium diet, with return of her renal function to baseline 12 days later; she was subsequently discharged.

COMMENT

The most important adverse effect of roentgenographic contrast media, apart from anaphylaxis, is acute oliguric renal failure. This phenomenon has been described in high-dose urography and more recently in other forms of angiography,[4] with a higher incidence in dehydrated or azotemic patients and in patients with multiple myeloma. The renal failure is usually noted as oliguria or as an acute rise in the level of serum creatinine within 12 to 24 hours of the procedure, and it is unresponsive to volume expansion or diuretics. Renal failure usually lasts from one to three weeks, with return to baseline function in most cases with appropriate management. The four cases presented here conform to this pattern. All four patients were diabetics. Three of the four had preexistent impairment of renal function. All had a worsening of azotemia and oliguria within 24 hours of cerebral angiography, which reached a nadir in three to four days. Renal function improved in all except patient 1. None of the patients suffered hypotension, and laboratory studies excluded other causes of acute renal failure such as myoglobinuria or hyperuricemia. The possibility of a cerebral event causing alteration of renal cortical blood flow and subsequent ischemia and renal failure has been suggested.[5,6] However, as discussed by Woods and Williams,[7] repeated experimental studies have been unable to demonstrate sustained renal ischemia induced via neurogenic pathways. Moreover, scrutiny of the published cases suggests other causes, such as fat emboli, hypotension, and dehydration, and leaves this entity in serious question.

The incidence of contrast-medium-induced renal failure is low.[8-10] Port and colleagues[4] reported only eight cases among 7,400 patients undergoing angiographic procedures. Such estimates may be misleading, for they fail to consider the incidence in a subgroup of patients who frequently need cerebral angiographic study. These are patients with hypertension, diabetes, and elderly patients with nephrosclerosis who may be comatose and dehydrated when they undergo emergency angiography. As with our patients, they frequently receive large amounts of contrast medium. Port et al[4] reported that half of their patients with renal failure received an amount close to the suggested upper limit of 5 mg/kg; it is worthwhile to note, however, that there are no convincing data in humans for an upper-dose limit.

Several mechanisms have been suggested for acute tubular damage in this entity, including precipitation of urinary Tamm-Horsfall mucoproteins[11] or myeloma paraprotein,[12] and hyperuricemia due to competition for excretion with contrast media[13] or hypersensitivity angiitis. None adequately explains the renal toxicity observed in our patients. More likely, it may be direct toxic effect of contrast materials on renal tubular epithelium. Experimental data by Talner and Davidson[14] indicate that the concentration of dye in the distal nephron is the most important factor, thus explaining the tendency toward damage in patients with low glomerular filtration rate due to dehydration or intrinsic renal disease. It also explains the effect of high doses of contrast medium.

Adequate hydration before the study and minimal dosages of contrast material may protect high-risk patients. It has been suggested that prophylactic mannitol be administered intravenously during extended roentgenographic procedures to increase urine flow.[4] Such a protocol employed at our hospital[15] for renal failure of recent onset uses an ampule of mannitol (12.5 gm) infused over ten minutes. If the cardiovascular function is adequate, urine flow will increase to 50 ml/hr for the next several hours. Furosemide should be avoided because the drug aggravates preexistent hypovolemia. Monitoring of urine flow and serum creatinine level for the 24-hour period after angiography in high-risk patients will assure the early detection of any compromise of renal function and allow more prompt institution of therapy.

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Somatic Anxiety Attacks and Propranolol

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• Patients with acute anxiety-like attacks are often evaluated for various medical conditions, and, when nothing is found, their symptoms are attributed to psychogenic causes. "β-Adrenergic hyperactivity" should be considered in these patients. Six patients are described who, we believe, are suffering from this condition. Low rates of isoproterenol hydrochloride infusion-precipitated symptoms that mimicked their spontaneous somatic anxiety attacks. Treatment with propranolol hydrochloride produced long-term symptomatic relief.

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Several investigators have recently reported the beneficial effect of propranolol hydrochloride, a β-adrenergic blocking agent, on anxiety.[1-3] This drug often suppresses many of the somatic manifestations of anxiety, such as tachycardia and tremor, even though the central feelings of anxiety are not usually ameliorated.[1,3] Most reports have dealt with chronic anxiety, either psychic or somatic, rather than acute anxiety attacks.

Frohlich and associates[4,5] described 14 patients with the "hyperdynamic β-adrenergic circulatory state." The complaint common to all of their patients was the sensation of cardiac awareness appearing as attacks of palpitations, chest discomfort, and tachycardia. The patients were studied to exclude pheochromocytoma, thyrotoxicosis, and porphyria as causes of these symptoms. Cardiac index and heart rate were found to be notably elevated. Additionally, autonomic function was tested and shown to be normal by determining blood pressure and pulse rate, response to tilt, Valsalva maneuver, cold pressor test, carotid sinus massage, and response to administration of levarterenol bitartrate, tyramine, and atropine sulfate. The only significant abnormality noted was with an intravenous infusion of isoproterenol hydrochloride during which, at a rate of 3μg/min, the heart rate increased more in the patients in a hyperdynamic β-adrenergic state than in the normal subjects. This change in heart rate, though apparently significant in itself, was accompanied, in two thirds of the patients, by a prompt, almost uncontrollable, hysterical outburst, reproducing the spontaneous attacks. These symptoms were reversed by intravenously administered propranolol, but not by placebo. These patients were then treated on a long-term basis with propranolol given orally, resulting in relief of the attacks.

We have evaluated six patients with β-adrenergic hyperactivity in whom the acute anxiety element predominated over the cardiovascular element of the attack. This communication reports the evaluation and treatment of these patients.

REPORT OF CASES

Case 1.—Eight years previously, a 27-year-old man began experiencing attacks consisting of a "surging," frightened feeling, with quickening of his pulse, tremulousness, and shortness of breath followed immediately by intense nervousness that lasted three minutes to as long as an hour. At the end, he was weak and exhausted for another hour. The attacks occurred as frequently as several times per week. He felt that he was more high strung than most people, but did not relate his attacks to emotional provocation, nor could we elicit a history of precipitating psychogenic factors. One of the patient's three brothers had had almost identical attacks, but they had lasted only two years, and then had ceased when he changed his job.

Findings from physical examination were normal. Levels of serum T_4 and urinary 5-hydroxyindole acetic acid (5-HIAA) and vanillylmandelic acid (VMA) were normal.

Case 2.—Seven years previously, a 47-year-old woman developed episodes of intense "nervousness," palpitations, flushing, sweating, tremulousness, and mild dizziness. The episodes occurred at any time and in any setting, but usually when she lay supine; they were partially relieved by sitting or standing. She almost constantly felt that she was on the verge of an attack, "like a slight one most of the time." Recently, attacks occurred daily and lasted from ten minutes to three hours. There was no past history of psychiatric or neurological disease.

Findings from physical examination were normal, except that the patient often appeared apprehensive, flushed, slightly diaphoretic, and mildly tremulous. Normal results were obtained from laboratory studies, including thyroid function tests, urinary 5-HIAA and VMA, urinary catecholamines, and a five-hour glucose tolerance test. Electrocardiogram monitoring during two attacks demonstrated a sinus tachycardia.

Case 3.—Three years previously, a 47-year-old man began experiencing attacks every one to four weeks, consisting of the sudden onset of intense "nervousness." He felt his heart "pounding and racing," became nauseated, diaphoretic, and dyspneic and experienced tingling in his arms. Frequently, he would vomit, and the episode would subside after 20 to 30 minutes. There was no present, past, or family history of neurological or psychiatric significance.

Findings from physical examination were normal. Normal results were obtained from laboratory studies, including thyroid function, urinary 5-HIAA and VMA, and monitoring of the ECG over an eight-hour period (during which the patient had no attacks).

Case 4.—During two pregnancies, seven years and one year previously, this 30-year-old woman began experiencing episodes of jitteriness, anxiety, cardiac awareness, and a strange sensation in the head, all of which were partially relieved by lying down. She was then well until five months previously when her episodic symptoms recurred and progressed until they began occurring daily. Each episode lasted one to two hours, though she often felt on the verge of an attack.

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Findings from physical examination were normal, and hyperventilation did not reproduce her symptoms. Results from laboratory studies were normal, including thyroid function tests, urinary 5-HIAA and VMA, five-hour glucose tolerance test, and ECG.

Case 5.—A 33-year-old woman, three months previously, began experiencing episodes of vague abdominal discomfort, heaviness in the chest, pounding of the heart, paresthesias of the extremities, generalized headache, and intense nervousness. The episodes lasted about two hours and were followed by a sense of fatigue. The attacks appeared unrelated to emotional stress.

Findings from physical examination were normal. Results of laboratory studies were normal, including 5-HIAA and VMA determinations.

Case 6.—A 33-year-old woman experienced episodes of generalized weakness, tightness and drawing in the neck and throat, difficulty breathing, tightness in the chest, and a sense of panic. The episodes lasted approximately ten minutes and frequently followed each other in close succession. They were associated with neither memory loss nor confusion. At times, she felt her heart racing. The episodes began in 1968, were relatively constant until 1971, then, after a period of relative infrequency, they recurred in 1973 and persisted until the present time. A variety of medications, including tranquilizers and phenytoin, had had no favorable effect.

Findings from physical examination were normal. The attacks could not be reproduced by hyperventilation. Laboratory evaluations including ECGs, electroencephalogram, and glucose tolerance test, were normal.

RESULTS

Isoproterenol Response

During a five-minute control period of intravenous infusion of saline, the blood pressure of patient 1 was 145/65 mm Hg, and the pulse rate was 81 beats per minute; he felt well. During the next five minutes, he received an infusion of 0.40μg/min of isoproterenol hydrochloride with no change in blood pressure or pulse rate; he remained well. During the next six minutes, the infusion rate was increased to 0.67μg/min of isoproterenol hydrochloride; blood pressure was 140/65 mm Hg, and pulse rate was 76 beats per minute. The infusion rate was then increased to 1.73μg/min. Average blood pressure for the next minute was 160/60 mm Hg, and average pulse rate was 124 beats per minute. Within 60 seconds, the patient experienced acute nervousness and shortness of breath. He was tremulous, flushed, and agitated and stated that this was a typical attack. Over the next three minutes, he received an intravenous injection of 4 mg of propranolol hydrochloride. This aborted his symptoms, and, for the next several minutes, blood pressure averaged 140/80 mm Hg, and pulse rate averaged 58 beats per minute.

Isoproterenol Hydrochloride Response

	Patient				
	1	2	3	4	5
Control pulse rate, beats/min	81	80	92	100	80
Isoproterenol hydrochloride infusion rate,* μg/min	1.73	2.0	2.6	2.0	0.5†
Pulse rate increase	43	60	37	38	20
Propranolol hydrochloride,‡ mg	4	5	3	4	2
Pulse rate after propranolol, beats/min	58	71	92	88	68

*Isoproterenol infusion rate represents that rate attained at the time the patient developed attack.

†Single injection in micrograms.

‡Total propranolol infusion dose required for complete relief of symptoms.

Patients 2, 3, and 4 underwent similar isoproterenol hydrochloride infusion tests, and acute attacks, virtually identical to their spontaneous ones, were precipitated at infusion rates of 2.0μg to 2.6μg/min. The attacks were aborted within two to three minutes by slow intravenous injection of propranolol.

Patient 5 was given a single intravenous injection of saline, with no response. She was then given a single intravenous injection of 0.5μg of isoproterenol hydrochloride after which she experienced an attack "identical" to one of her spontaneous attacks. Heart rate increased by 20 beats per minute. A 2-mg propranolol hydrochloride infusion aborted the attack. Fifteen minutes later, the saline and isoproterenol injections were repeated. Similar responses occurred, but the attack was less intense.

Patient 6 refused the isoproterenol infusion test.

The isoproterenol response data are summarized in the Table.

Treatment Response

All of these patients were first given propranolol hydrochloride at a dose of 30 or 40 mg daily administered in divided doses. None had a history of congestive heart failure, atrioventricular heart block, asthma, or diabetes. The dose was gradually increased until "anxiety attacks" ceased. The amount of propranolol hydrochloride required varied from 60 to 320 mg daily, with the average being 160 mg daily. During a 4- to 24-month follow-up period, these patients have been virtually free of further anxiety attacks. No attempt has yet been made to either discontinue propranolol treatment or to go to a double-blind crossover study with propranolol and placebo.

COMMENT

One sees many patients with episodic autonomic symptoms of palpitations, a racing heart, chest tightness, shortness of breath, rapid ventilation, tremulousness, sweating, flushing, dizziness, and an intense feeling of nervousness or anxiety.

These patients often are evaluated for hypoglycemia, hyperventilation syndrome, pheochromocytoma, carcinoid syndrome, thyrotoxicosis, and primary cardiac arrhythmia. When these entities have been satisfactorily excluded, the patient often is referred to a psychiatrist, because an anxiety reaction or some other functional condition is suspected. We believe that some of these patients suffer from a β-adrenergic hyperactivity state.

Frohlich et al[5] reported that the isoproterenol infusion test was a valuable aid in diagnosing this clinical condition. They found that incremental increases in the infusion rate of isoproterenol hydrochloride from 1μg/min to 3μg/min produced a minimal pulse rate change or "nervousness" in normal subjects, but, in patients considered to have a hyperdynamic β-adrenergic state, similar infusions resulted in a tachycardia and an anxiety attack of such intensity that some requested the test be terminated. The attack was stopped with propranolol given intravenously.

Other investigators have found that many normal people have notable elevations in heart rate at isoproterenol hydrochloride infusion rates of 1μg to 2μg/min,[6] and still others have reported considerable individual variability in the heart rate response to isoproterenol.[7,8]

Bourne and co-workers[9] critically reviewed the report of Frohlich et al[5] and directed attention to the discrepancy between the data of Frohlich and associates on isoproterenol-induced cardioacceleration and the data reported by others. They concluded that "... the isoproterenol infusion test must be standardized to make it useful in selecting a group of patients for study."[9]

Although isoproterenol hydrochloride infusions are generally safe,[5] low-dose infusions (1μg to 2μg/min) have been shown routinely to produce ischemic electrocardiographic changes in patients with coronary artery disease. The isoproterenol infusion test has even been advocated as a stress test for predicting the presence or absence of coronary artery disease.[10,11] Thus, it would seem prudent to electrocardiographically monitor any patient undergoing the test.

We are not able, on the basis of our data, to resolve the issue of whether or not the isoproterenol infusion test is specifically diagnostic for this group of patients in terms of the heart rate response. We were, however, impressed that the infusion precipitated acute anxiety attacks in the patients tested. This was not noted in any of the normal subjects reported in the literature even when there was substantial cardioacceleration.[5,6,11]

The pathophysiology of the β-adrenergic hyperactivity state is not yet clear. Some investigators favor an increased responsiveness of peripheral β-adrenergic receptors.[2,12,13] A direct central nervous system mechanism has not been ruled out.[14] The relationship between the somatic symptoms and the emotional sensation of anxiety, in normal people and in those with β-adrenergic hyperactivity, is also not clear. It would be interesting to study the effect of propranolol on patients with attacks of anxiety precipitated by obvious emotional stress.

Bourne et al[9] were critical of the use of propranolol in the treatment of patients with the hyperdynamic β-adrenergic state largely on the grounds that propranolol has known potentially hazardous side effects and "... when the natural history of the disease is further studied, it may be found that no treatment is necessary to improve longevity and productivity in patients." We believe that Bourne and co-workers have placed excessive emphasis on the hazards of treatment relative to the "varying degrees of physical limitation" noted by Frohlich et al[5] and the intense, repetitive emotional discomfort experienced by our patients. It is important to recognize the hazards of using propranolol in patients with congestive heart failure, atrioventricular heart block, asthma, and diabetes. We agree with the concern of Bourne and associates regarding the need for a controlled therapeutic trial showing propranolol to be more effective than other, less hazardous therapy, including placebo.

We believe that the six patients described suffer from β-adrenergic hyperactivity, and in none of them was this possibility considered initially. The isoproterenol infusion test gave a positive response in each of the patients tested, and this led to a therapeutic trial of propranolol. The treatment was highly effective in all patients. We are not advocating, however, the use of propranolol in the treatment of chronic anxiety states.

Sergio Rabinovich, MD, provided criticism, and Coni J. Hupp assisted in the preparation of this article.

Nonproprietary Name and Trademark of Drug

Propranolol hydrochloride—*Inderal.*

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Late-Onset Acid Maltase Deficiency

Detection of Patients and Heterozygotes by Urinary Enzyme Assay

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• Daily urinary excretion of acid maltase (12.78 ± 2.10 units/24 hr/mg of creatinine, in 11 normal adults) was significantly decreased in ten patients with late-onset acid maltase deficiency (1.33 ± 0.16 units/24 hr; $P < .001$) and 11 heterozygotes (3.27 ± 0.62 units/24 hr; $P < .001$). Maximal inhibition of urinary acid maltase activity by antibodies against human placental enzyme was 53% in controls, 30% in heterozygotes, and virtually absent in patients.

Investigation of pH curves and enzyme inhibition by antibodies confirmed the presence in the kidney of an immunologically distinct "extra" maltase enzyme active at acid pH. Whether acid maltase in normal urine originates in the kidney or cells of the lower urinary tract, the enzyme defect seems to be expressed in these cells in late-onset acid maltase deficiency.

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Diagnosis of the infantile, generalized form of acid maltase deficiency (AMD, glycogenosis type 2, Pompe disease) is relatively simple because of the characteristic clinical picture: profound weakness and hypotonia, hepatosplenomegaly, severe cardiomegaly, and, sometimes, macroglossia. Muscle biopsy specimen shows massive glycogen storage.

In the late-onset variant of AMD, however, the clinical picture is limited to skeletal muscle and cannot be distinguished from other, more common muscle disorders such as muscular dystrophy or polymyositis.[1,2] Glycogen accumulation varies but is less pronounced than in the infantile form, making morphological diagnosis difficult in routine muscle biopsy specimens. In leukocytes, enzyme activity is either normal[3-5] or only partially deficient[6-8]; this makes detection of patients difficult and detection of heterozygotes virtually impossible. Analysis of the maltase system in urine provides a simple and reliable tool for the identification of patients and heterozygotes in late-onset AMD.

PATIENTS AND METHODS

In ten patients (six men, four women; aged 16 to 50 years) the diagnosis of late-onset AMD was confirmed by morphological and biochemical studies of muscle biopsies. With the artificial substrate 4-methylumbelliferyl α-D-glucoside (MUαG), muscle acid maltase activity varied from 2.4 to 12.2% of normal.[8] Urine was collected for a 24-hour period in the cold (4 C) without preservatives, the volume measured, and an aliquot frozen and kept at −20 C until the time of assay.

Urine samples were obtained in the ten patients, seven definite heterozygotes (children or parents of patients), four possible heterozygotes (two siblings, one aunt, and one uncle), 11 healthy adult controls (seven men, four women; aged 23 to 68 years), and four healthy children, 4 to 15 years of age (three boys, one girl). Creatinine was measured by the method of Peters.[9] Some urine samples (30-ml aliquots) were centrifuged at 27,000 g in the cold, the supernatants decanted and the pellets resuspended and homogenized in small volumes (1.6 ml) of distilled water in all-glass homogenizers.

Kidneys were obtained at autopsy from a 4-month-old baby with generalized AMD, a baby of the same age with trisomy 21, and two adult patients with no renal or neuromuscular disease. Portions of ureter and urinary bladder were also obtained from the same adults. Tissues were frozen and stored in liquid nitrogen. Homogenates were prepared in distilled water in all-glass homogenizers in the cold.

Maltase activity was measured between pH 3.5 and 7.0 by the method of Galjaard et al.[10] The incubation mixture contained, in a final volume of 0.4 ml:0.1M acetate buffer, 1.4 mM MUαG, and 100μl of urine or 20μl of tissue extracts (containing 0.1% octoxynol-9 [Triton X-100]). After one hour of incubation at 37 C, 1.6 ml of 1.0M glycine-Na carbonate buffer (pH, 10.0) was added and the fluorescence of liberated umbelliferone measured in a spectrofluorometer.

Acid maltase was purified from human placenta by the procedure of deBarsy et al.[11] The purified enzyme had approximately 13,000-fold higher specific activity than the crude extract, and showed only two protein bands on sodium dodecyl sulfate-acrylamide gel electrophoresis (our unpublished observations). Two aliquots of enzyme preparation (0.2 mg of protein mixed with Freund complete adjuvant) were injected intradermally in a rabbit at a month's interval. Two weeks after the

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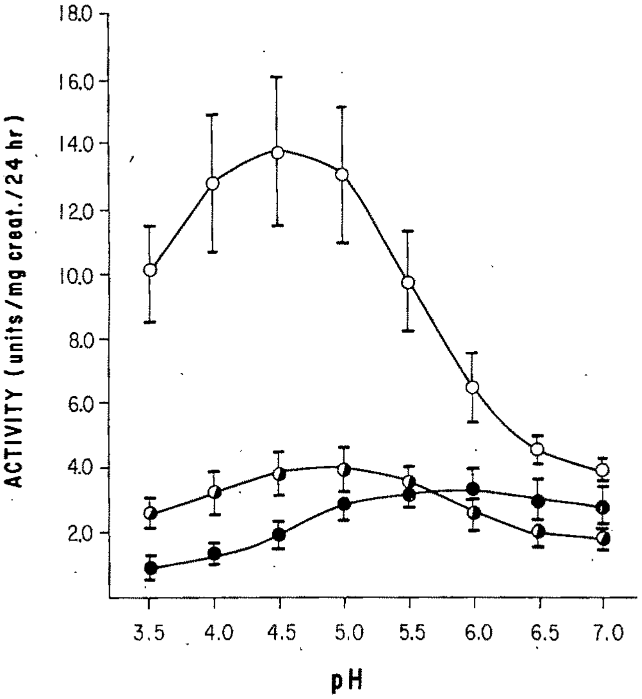

Fig 1.—pH curves of urinary maltase (daily excretion/mg of creatinine ± SD) in late-onset AMD patients (solid circles), heterozygotes (half-open circles), and controls (open circles).

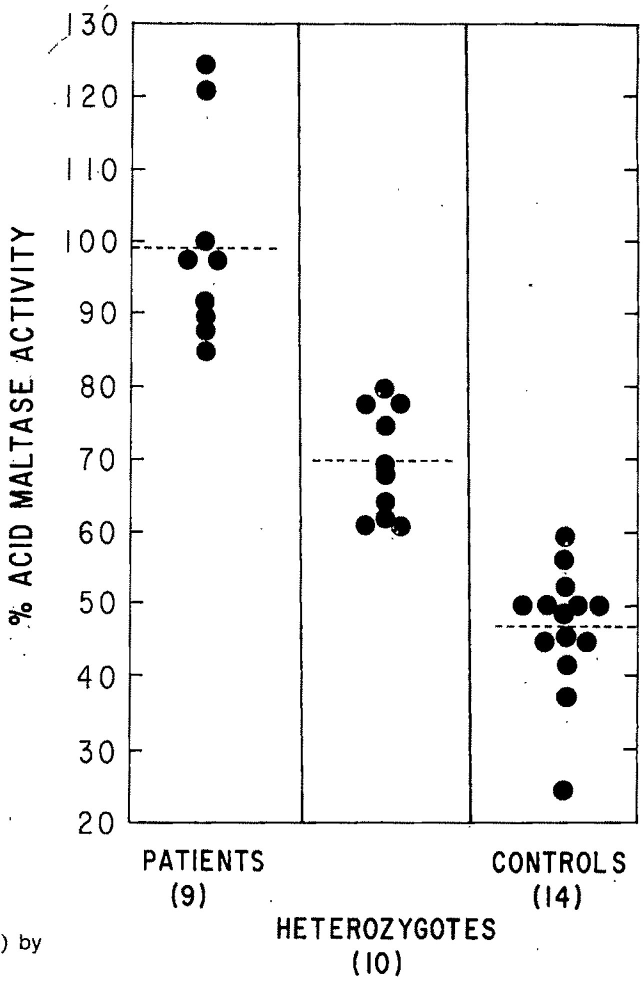

Fig 2.—Maximal inhibition of urinary acid maltase (pH 4.0) by antibodies against human placental enzyme.

Daily Urinary Excretion of Acid Maltase in Late-Onset Acid Maltase Deficiency

	Acid Maltase, Units (MUαG*)/24 hr/mg Creatinine		
	pH 4.0†	**pH 6.5**	**pH 4.0/pH 6.5**
Patients (N = 10)	1.338 ± 0.160	3.021 ± 0.673	0.44 ± 0.12
Heterozygotes (N = 11)	3.276 ± 0.623	2.170 ± 0.382	1.51 ± 0.32
Controls (N = 11)	12.78 ± 2.10	4.557 ± 0.430	2.80 ± 0.46

*4 = methylumbelliferyl α-D-glucoside.

†Statistical significance (Student *t* test): patients vs controls, $P < .001$; heterozygotes vs controls, $P < .001$; patients vs heterozygotes, $P < .001$.

second injection, the animal was exanguinated and the immune serum stored in aliquots at −20 C. Enzyme inhibition studies were performed by preincubating urine or tissue extracts (at 37 C for 30 minutes) with increasing amounts of diluted antiserum until maximum inhibition was achieved. Samples incubated with normal rabbit serum served as controls.

RESULTS

In the acid range, pH profiles of urinary maltase activity were significantly different in patients, heterozygotes, and controls (Fig 1). Mean maltase activity at pH 4.0 was only 10% of normal in the patients' urine and 26% in the urine of heterozygotes (Fig 1). Neutral maltase activity was essentially unchanged; this was reflected by a shift of pH optimum from 4.5 in the urine of controls to 4.9 in heterozygotes and 5.8 in patients. As a result, ratios of acid (pH 4.0) to neutral (pH 6.5) maltase activity were highly significant in discriminating the three groups (Table).

When referred to 24-hour excretion and creatinine concentration, there was relatively little variability in daily excretion of acid maltase in adult controls, independent of sex (Fig 1 and Table). However, in children below age 16, we found consistently lower acid maltase excretion, in the range of adult heterozygotes (2.89 units/24 hr/mg of creatinine in four children, 4 to 15 years of age). In spite of this, two affected children (an 8-year-old patient and a heterozygote of the same age) could be identified on the basis of activity at pH 4.0 (patient, 1.04; heterozygote, 2.11), acid to neutral activity ratio, and pH optimum.

Urine samples lost less than 10% of enzymatic activity in five weeks despite repeated freezing and thawing, and there was little variation of maltase activity between samples obtained at different times from the same person. Urine pH varied between 5.24 and 8.40 (mean, 6.04) and

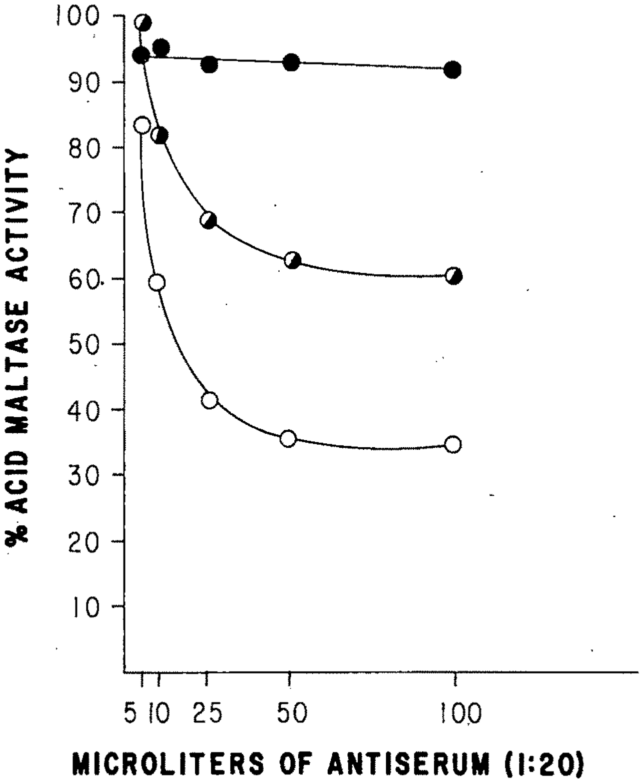

Fig 3.—Inhibition curves of urinary acid maltase (pH 4.0) by antiplacental antibodies in patients (solid circles), heterozygotes (half-open circles), and controls (open circles).

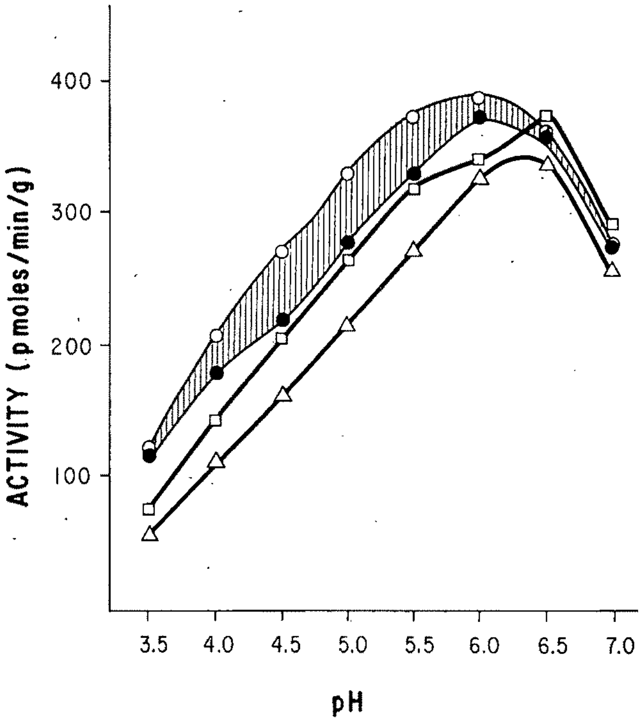

Fig 4.—pH curves of renal maltase activity in a patient with infantile AMD (triangles), a normal infant (squares), and a normal adult (open circles). Solid circles represent adult kidney maltase activity after maximal inhibition by antibodies. Shaded area shows degree of inhibition.

there was no significant difference between patients, heterozygotes, and controls. Centrifugation of six urine samples at 27,000 g resulted in mean loss of 2% maltase activity in both acid and neutral pH ranges.

Maximal inhibition of urinary acid maltase by antibody to placental enzyme also separated the sample population into three non-overlapping groups (Fig 2). Acid maltase activity was inhibited 53% in the urine of controls, but about 30% in heterozygotes, and was essentially not affected at all in the patients (Fig 3). Although the degree of inhibition was different in heterozygotes and controls, the shape of the curve was similar (Fig 3).

To evaluate the contribution of various tissues to urinary acid maltase, the kidney, ureter, and urinary bladder were studied. Maltase activity was high in human kidney, with pH optimum 6.0 (Fig 4). Inhibition by antibodies to placental acid maltase occurred between pH 4.0 and 5.5, but did not exceed 23% (Fig 4, shaded area), while it was approximately 50% in extracts of bladder and ureter.

The pH profile of maltase activity in the kidney of a 4-month-old baby with generalized AMD did not differ significantly from an age-matched patient with trisomy 21 or from an adult control (Fig 4). However, while acid activity in the kidney of the trisomy infant was inhibited by antibody as much as in normal adult tissue, no inhibition was found in the kidney of the AMD infant.

COMMENT

Although rare, late-onset AMD is important in differential diagnosis. The clinical picture is characterized by weakness of trunk and proximal limb muscles. Respiratory muscles are often involved, resulting in ventilatory insufficiency. Weakness begins in childhood or adult life, and progression is generally slow. The serum creatine phosphokinase level is consistently elevated, and electromyography shows myopathic features with myotonic discharges.[2] However, none of these characteristics is specific and the disorder is often misdiagnosed as progressive muscular dystrophy in children and polymyositis or "limb girdle" dystrophy in adults. An accurate differential diagnosis has more than academic value, because both prognosis and therapy are different in late-onset AMD. Except for cases with severe respiratory insufficiency, prognosis tends to be more benign in AMD than in dystrophies or polymyositis. Therapy with corticosteroids, often effective in polymyositis, is not indicated in AMD, while it has been suggested that a ketogenic diet may slow down the accumulation of glycogen.[2]

Until now, definitive diagnosis of late-onset AMD required measurement of the enzyme in muscle. The use of leukocytes in diagnosis is limited because enzyme activity is either normal[3-5] or only partially deficient.[6-8] Detection of heterozygotes by leukocyte studies is even more difficult, and muscle biopsy is rarely considered in these clinically normal persons. Therefore, we sought alternatives, and a report of decreased acid maltase in the urine of two infants with generalized AMD[12] suggested that a similar defect might be found in late-onset cases. The marked decrease of urinary acid maltase excretion that we actually found in ten adults with late-onset AMD shows that this is a sensitive and reliable diagnostic test. Heterozygotes could also be reliably detected by urinary assay, and this may be useful in genetic counseling. The defect of acid but not neutral maltase activity was reflected in a shift of optimum pH towards the neutral range, and in a decrease of the acid to neutral activity ratio. Both parameters can be used to identify patients and heterozygotes.

These results were obtained in adults with AMD. In four normal children, daily urinary excretion of acid maltase was substantially less than in normal adults. Therefore, differences between patients, heterozygotes, and controls were not as clear-cut in children as in adults. Two affected children, one patient and one heterozygote, were recognized, but a larger series is needed to assess the value of the urinary assay in childhood AMD.

There are three major sources of urinary enzymes: serum, kidney, and epithelial cells of the urogenital tract.[13] Serum is not a likely source of urinary acid maltase because the enzyme activity in serum is very low[12,14] and the molecular weight of about 110,000[11,15] is too high to allow glomerular filtration.[13] To evaluate the possible renal origin of the urinary enzyme, we compared the pH profile and immunological characteristics of maltase in urine and kidney.

Human kidney has a unique maltase system.[4,16,17] Maltase activity is very abundant but does not show the two peaks of activity, at acid and neutral pH, that are characteristic of most other tissues; instead, there is a single peak at pH 6.0. This peculiar pH profile may be due to the presence in kidney of a third maltase enzyme active over a broad pH range in addition to the usual acid and neutral maltases. This is supported by three lines of evidence: (1) Inhibition of maltase by turanose was only 33% in kidney but approximated 90% in other tissues.[16] (2) An extra band of acid activity was seen in electrophoretic studies with kidney extract.[17] (3) Maltase activity was found at acid pH in kidney of infants with generalized AMD.[4,16] The presence of an "extra" maltase enzyme in human kidney was confirmed in the present investigation by immunological studies. Antibodies against placental acid maltase inhibited enzyme activity by 50% to 60% in several tissues (muscle, placenta, urinary bladder), but only by 23% in normal kidney. Maltase activity at acid pH was present in the kidney of an infant with generalized AMD, as in previous studies,[4,16] and was not inhibited by antibodies.

Unlike the kidney, the pH profile of maltase in normal urine showed a large peak of activity at pH 4.5. Also, maximal inhibition of urinary maltase activity by antiplacental acid maltase antibodies was about 50%, as in other tissues, including ureter and urinary bladder, but twice the inhibition of the renal enzyme. There are two possible interpretations of these findings: (1) Most urinary maltase activity originates in the mucosa of the urogenital tract, rather than in the kidney. (2) The contribution of kidney to urinary maltase in normal individuals may be primarily lysosomal acid maltase. Different patterns of subcellular localization or binding to membranes (endoplasmic reticulum or Golgi apparatus) may explain the lesser tendency of both neutral and "extra" renal maltases to leak into the urine.

However, a small amount of the urinary maltase, active at acid pH, probably corresponds to the "extra" renal enzyme. This is suggested by the presence, in urine of late-onset AMD cases, of acid maltase activity that is not inhibited by antibodies, and by the intermediate degree of inhibition in the urine of heterozygotes. Regardless of the precise source of urinary acid maltase, the marked decrease of activity in patients and heterozygotes is indirect evidence that still another tissue, besides muscle, liver, leukocytes, and fibroblasts in culture,[2] manifests the enzyme defect in late-onset AMD.

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Neonatal Encephalopathy Following Fetal Distress

A Clinical and Electroencephalographic Study

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• Twenty-one neonates of over 36 weeks' gestation suffered perinatal asphyxia but not chronic hypoxia. Three clinical stages of postanoxic encephalopathy were distinguished. Stage 1 lasted less than 24 hours and was characterized by hyperalertness, uninhibited Moro and stretch reflexes, sympathetic effects, and a normal electroencephalogram. Stage 2 was marked by obtundation, hypotonia, strong distal flexion, and multifocal seizures. The EEG showed a periodic pattern sometimes preceded by continuous delta activity. Infants in stage 3 were stuporous, flaccid, and brain stem and autonomic functions were suppressed. The EEG was isopotential or had infrequent periodic discharges.

Infants who did not enter stage 3 and who had signs of stage 2 for less than five days appeared normal in later infancy. Persistence of stage 2 for more than seven days or failure of the EEG to revert to normal was associated with later neurologic impairment or death.

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Ischemic-anoxic encephalopathy is the most common neurologic disease of the perinatal period, and is a major cause of chronic disability in childhood. A variety of changing clinical and electroencephalographic manifestations occur in the hours and days subsequent to disturbances in placental or fetal circulation and lack of oxygen during labor or at the time of delivery. The effects of ischemia and hypoxia may not be identical, but they are difficult to separate clinically, and both factors probably contribute to encephalopathy in distressed fetuses. Clinical evaluation is further impeded by secondary postnatal complications, such as hypoglycemia and hypocalcemia, which are closely related to and not independent of perinatal asphyxia.

This study attempted to provide a systematic clinical approach to the identification of those transitory neurologic signs that appear sequentially following asphyxia near or at the time of birth, and to suggest a relation of the duration of these signs to prognosis. The severity of a perinatal insult is difficult to quantitate, but the postnatal course of the infant, together with EEG changes, appear to offer the best indication of later neurologic impairment.

METHODS

Twenty-one infants were studied (Table 1). All were over 36 weeks' gestational age at birth and none had evidence of congenital heart disease, traumatic cerebral injuries, hydrocephalus, or infection. Each infant had a well-defined episode of fetal distress or an Apgar score of 5 or less at one or five minutes after delivery. In no case could the infant's clinical state be attributed to drugs administered to the mother. Infants with meconium aspiration, respiratory distress syndrome, or other illness resulting in chronic, continuing hypoxia were excluded. Respiratory assistance was required only in some of the most severely involved infants, but repeated determinations of blood Po_2, Pco_2, and pH indicated adequate ventilation. Infants with transitory hypoglycemia or hypocalcemia were not excluded because these common metabolic alterations are considered part of the neonatal postanoxic syndrome.

Glucose, calcium, magnesium, and electrolyte levels in serum were determined within an hour after admission. Infants unable to maintain adequate oral intake were fed by gavage or treated with intravenous fluids for a few days. Antibiotics were administered to a few infants because of suspected sepsis, but all blood cultures were negative. Serial microbilirubin determinations were made in icteric infants. Seizures were treated with phenobarbital administered intravenously every 12 hours for a total daily dose of 10 mg/kg

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of body weight. The daily dose was decreased by half after the infant had remained free of seizures for 24 to 48 hours. Phenobarbital was withheld from infants without seizures.

Serial neurologic examinations were performed at 12 to 24 hourly intervals for the first six days, and every other day thereafter until hospital discharge, usually at 2 to 3 weeks of age, or until death in a few cases. Neurologic examination included evaluation of level of consciousness, corneal and gag reflexes, autonomic functions, cranial nerves, muscle tone and activity, tendon stretch reflexes, tactile reflexes, suck, Moro, and tonic neck responses, and oculovestibular reflex. Response to pinprick was tested first in the pretibial region, a high-threshold zone, and then on the plantar surface, a low-threshold zone, on each side. The circumference of the head was measured and the fontanelles palpated. Ocular fundi were examined.

Electroencephalograms were recorded using the International 10-20 System of electrode placement, with modified montages that doubled the interelectrode distances used in routine adult recordings. A record was made as soon as possible after admission to hospital, again in 24 hours, and then every three to five days until the infant was discharged. Both wakefulness and sleep were sampled when the infant's level of consciousness allowed this distinction. One EEG channel was devoted to electrocardiographic monitoring during most of the recording.

Follow-up neurologic examinations and EEGs were performed at 3, 6 or 9, and 12 months of age, or more frequently in a few cases. The criteria for "normal" at a given age were based on the achievement of skills within a month of the 50th percentile in the Denver Developmental Screening Test for Infants, with appropriate allowances made for infants born at less than 40 weeks' gestation. Additional criteria for normal were the absence of hemiparesis or other focal neurologic deficits, the presence of normal muscle tone and reflexes, and a normal EEG.

RESULTS

Clinical Features

Three clinical stages of neonatal encephalopathy were distinguished, and are summarized in Table 2. Of the 21 infants, only seven exhibited features of stage 1, all had characteristics of stage 2, and six infants passed through stage 3. The duration of stage 1 ranged from 1½ to 18 hours. Stage 2 lasted a mean of 4.7 days, excluding two infants who showed features of this stage for three and nine weeks. Duration of stage 3 ranged from a few hours to four weeks. Recovery from stage 2 was heralded by disappearance of myoclonus and of parasympathetic discharge (defined below), increased alertness, an improved suck, and reversion of the EEG from a periodic pattern to one of continuously similar activity in wakefulness. Improvement in the EEG preceded the resolution of clinical signs of stage 2.

An attempt was made to define level of consciousness by as many of Plum's and Posner's criteria[1] as are applicable at this age. "Hyperalertness" described infants in full wakefulness who indeed did not sleep for up to 24 hours. The eyes were widely open and the infants appeared to be staring, with a decreased frequency of blinking. Visual tracking responses were not enhanced, however. Spontaneous motor activity was normal or decreased, but they had a lowered threshold to all types of minimal stimuli. A Moro reflex was easily elicited with light tactile stimuli to the trunk, a bright light, a sudden sound of moderate loudness such as a voice, or even odors placed under the nostrils. It also occurred seemingly spontaneously, in response to proprioceptive stimuli associated with the infant's own sudden movements.

"Lethargy" was defined as a state of slightly delayed but complete responses to stimuli, a slightly increased threshold for eliciting such responses, and a decreased amount of spontaneous movements. "Obtundation" was the term applied to infants with delayed and incomplete responses, a markedly increased threshold to all sensory stimuli, and little or no motor activity. Lethargic and obtunded infants also were irritable when disturbed. "Stuporous" infants were those who responded only to strong, noxious stimuli by withdrawal of the extremity or by assuming a decerebrate posture, had absent corneal and gag reflexes, and who often required assisted respirations because of shallow, ataxic breathing with frequent apneic spells. Actual coma was rare in the newborn. Spinal withdrawal reflexes were preserved in even the most severely depressed infants.

Rhythmic segmental myoclonus was seen as a coarse 4- to 7-hertz tremor occurring in an extremity or occasionally involving facial muscles asymmetrically without deviation of the head and eyes. The tremor was generated in proximal muscles and usually was not synchronous on the two sides, but continually shifted focus. It was enhanced by sudden movement of an extremity. A light tap on the patellar ligament or brachioradialis tendon often elicited a clonic reflex that lasted several seconds and increased in amplitude before decreasing.

Characteristic postures were observed. The distal joints, fingers and toes, maintained the most consistently abnormal postures of strong flexion, and extension of the fingers was incomplete when they were stroked on the dorsal surface. The thumbs were strongly flexed, adducted, and opposed across the palms (ie, "cortical thumbs"). The wrists also were often flexed. These postures were enhanced by any type of stimulation. They were strongest in stage 2. Decerebrate posturing was seen only in stage 3, and usually was intermittent and precipitated by nonspecific stimuli. The spine extended in opisthotonos. The elbows extended and the wrists pronated. The hips abducted rather than extended as they do in decerebrate adults, a feature probably more related to anatomic differences between the hips of newborn infants and adults than to differences in brain stem mechanisms.

Changes in autonomic function constituted some of the most dramatic contrasts between the stages. Stage 1 was accompanied by generalized activation of the sympathetic nervous system, manifested by mydriasis, tachycardia, and increased alertness. Stage 2, in contrast, was characterized by generalized parasympathetic effects. Pupils were tiny even in dim light. The heart rate was abnormally slow, with only occasional increases to over 120 beats per minute. Secretions were often copious, obstructing respiratory pathways and requiring frequent suctioning. Gastrointestinal motility was increased and peristalsis could be heard over the abdomen. Some infants passed large, green, watery stools. Stage 3 appeared to be accompanied by suppression of both autonomic systems. The pupils were small to midposition, often unequal, and responded poorly to light. Infants in stage 3 also lost body temperature regulation and were often hypothermic despite external warming.

Seizures occurred in about half of the patients and were almost exclusively limited to stage 2. None occurred in stage 1 and only rarely were they seen in stage 3. The seizures occurred on the first or second day after birth and in every case were focal or multifocal, both clinically and electroencephalographically. Status epilepticus did not occur. The seizures were easily controlled with phenobarbital. The rate of recovery did not appear to be affected by the administration of this drug, and the criteria of stage 2 were recorded before phenobarbital was given.

Electroencephalographic Features

In stage 1 the EEG was interpreted as normal in wakefulness. The first alteration occurred early in stage 2, usually in the first 24 hours. It consisted of voltage depression of 5μv to 25μv activity in the delta and low-theta frequency range, and a paucity of the normal amount of upper theta and alpha range activity usually found in the normal full-term waking EEG (Fig 1). The low amplitude slowing was often slightly more pronounced in one temporal region than the other, but was generalized.

A periodic pattern in wakefulness or obtundation was seen in some infants in stage 2 from birth, or appeared on the second day in most of those who initially had low amplitude slow activity. Polymorphic sharp and slow waves of 50μv to 200μv occurred in bursts lasting one to three seconds, and alternated with a low-amplitude delta and theta phase lasting three to six seconds (Fig 2). "Premature ripples" of 16 to 20 Hz were superimposed in both phases at times. The high-amplitude phase occurred simultaneously in both hemispheres, but was not synchronous.

Patient/Age, wk*/Sex	Birth Weight, gm	Delivery	Fetal Distress
1/40/F	3,175	Breech	Not documented; infant required intubation at birth
2/37/M	2,420	Spontaneous vaginal, vertex presentation	Abruptio placentae; infant required intubation at birth
3/40/M	2,835	Spontaneous vaginal, vertex presentation	Not documented; infant required intubation at birth
4/38/M	2,948	Emergency cesarean section	Fetal tachycardia; meconium-stained amniotic fluid; umbilical cord around infant's neck
5/42/M	4,139	Spontaneous vaginal, vertex presentation	Fetal bradycardia; meconium-stained amniotic fluid; head in vagina two hours; infant required intubation at birth
6/39/M	3,204	Precipitous vaginal, vertex presentation	Head delivered spontaneously before arrival at hospital
7/39/M	3,005	Elective cesarean section	Not documented; infant required intubation at birth
8/39/F	2,892	Elective cesarean section	Not documented; cardiac arrest at one to two hr after birth
9/40/F	3,005	Spontaneous vaginal, vertex presentation	Meconium-stained amniotic fluid
10/41/F	3,402	Spontaneous vaginal, vertex presentation	Meconium-stained amniotic fluid
11/44/F	2,920	Spontaneous vaginal, vertex presentation	Meconium-stained amniotic fluid; postmaturity; umbilical cord around infant's neck
12/40/F	3,742	Spontaneous vaginal, vertex presentation	Fetal bradycardia
13/40/F	3,800	Elective cesarean section	Not documented; infant required intubation at birth
14/40/M	3,575	Emergency cesarean section	Fetal bradycardia; abruptio placentae; umbilical cord around infant's neck
15/40/F	3,771	Elective cesarean section	Fetal bradycardia; meconium-stained amniotic fluid; postmaturity; umbilical cord around infant's neck; infant required intubation at birth
16/40/F	2,892	Spontaneous vaginal, vertex presentation	Meconium-stained amniotic fluid
17/37/M	3,640	Spontaneous vaginal, vertex presentation	Fetal bradycardia
18/40/M	3,374	Elective cesarean section	Meconium-stained amniotic fluid
19/44/F	4,026	Spontaneous vaginal, vertex presentation	Meconium-stained amniotic fluid; postmaturity
20/38/M	3,127	Spontaneous vaginal, vertex presentation	Fetal bradycardia; meconium-stained amniotic fluid; premature separation of placenta; umbilical cord prolapsed and contained hematoma
21/37/M	2,580	Breech	Fetal tachycardia

Table 1.—Perinatal Data and Outcome of Infants

Apgar Score, 1 min/5 min	Duration of Encephalopathy			Seizures	Abnormal Laboratory Data	Outcome
	Stage 1	Stage 2	Stage 3			
1/4	...	3 days	23 days	No	...	Stuporous until death at 27 days of age
0/1	...	9 wk	...	No	...	Died at 9 wk of age
2/3	...	1 day 3 wk†	3 days	Yes	...	Spastic diplegia; no development; myoclonic epilepsy at 6 mo; died at 8 mo of age
8/5	...	1 to 2 days	8 days	Yes	Blood glucose level, 38 mg/100 ml at 14 hr	Spastic diplegia; no development; myoclonic epilepsy; hypsarrhythmic EEG; died at 11 mo of age
0/4	...	...	8 days	Yes	Ventricular fibrillation at 2 days; renal failure	Spastic diplegia; no development at 9 mo of age
1/1	...	8 days†	...	Yes	...	Spastic diplegia; poor development; EEG slow dysrhythmic nonparoxysmal at 12 mo
...	...	5 days	1 day	No	...	Poor development at 6 mo of age
5/7	...	6 days	...	No	Diabetic mother; no hypoglycemia or hypocalcemia	Normal at 6 mo of age
...	14 hr	6 days	...	Yes	...	Normal at 6 mo of age
6/9	18 hr	6 days	...	Yes	Blood glucose level, 17 mg/100 ml at 6 hr	Mild developmental delay at 9 mo of age
5/7	...	6 days†	...	Yes	Blood glucose level, 25 mg/100 ml at 12 hr	Spastic diplegea; slow development; no seizures; EEG slow dysrhythmic nonparoxysmal at 6 mo of age
6/3	...	5 days	...	No	Left renal vein thrombosis	Normal at 6 mo of age
1/4	...	4 days	...	No	...	Normal at 6 mo of age
3/...	...	4 days	...	Yes	Blood glucose level, 13 mg/100 ml at 6 hr	Normal at 6 mo of age
3/3	...	6 days	...	No	Blood glucose level, 26 mg/100 ml at 6 hr; Ca++, 3.8; Mg++, 1.4 mEq/liter at 22 hr	Normal at 6 mo of age
6/8	6 hr	5 day	...	Yes	...	Normal at 9 mo of age
4/5	1½ hr	4 days	...	No	Diabetic mother; blood glucose level, 33 mg/100 ml, Ca++, 4.3, Mg++, 1.4 mEq/liter at 2 hr	Normal at 6 mo of age
4/7	3 hr	4 days	...	Yes	Blood glucose level, 36 mg/100 ml at 4 and 5 hr	Normal at 9 mo of age
7/6	18 hr	4 days	...	No	...	Normal at 7 mo of age
1/4	...	3 days	...	No	Ca++, 4.0; Mg++, 1.3 mEq/liter at 12 hr	Normal at 6 mo of age
9/10	12 hr	2 days	...	Yes	Ca++, 3.5 mEq/liter at 24 hr	Normal at 12 mo

*Estimated gestational age at birth.

†Recovery from stage 2 accompanied by EEG change from periodic pattern to abnormal continuous low-amplitude delta and theta activity instead of to normal.

Table 2.—Distinguishing Features of the Three Clinical Stages of Postanoxic Encephalopathy in the Full-Term Newborn Infant

	Stage 1	Stage 2	Stage 3
Level of consciousness	Hyperalert	Lethargic or obtunded	Stuporous
Neuromuscular control			
Muscle tone	Normal	Mild hypotonia	Flaccid
Posture	Mild distal flexion	Strong distal flexion	Intermittent decerebration
Stretch reflexes	Overactive	Overactive	Decreased or absent
Segmental myoclonus	Present	Present	Absent
Complex reflexes			
Suck	Weak	Weak or absent	Absent
Moro	Strong; low threshold	Weak; incomplete; high threshold	Absent
Oculovestibular	Normal	Overactive	Weak or absent
Tonic neck	Slight	Strong	Absent
Autonomic function	Generalized sympathetic	Generalized parasympathetic	Both systems depressed
Pupils	Mydriasis	Miosis	Variable; often unequal; poor light reflex
Heart rate	Tachycardia	Bradycardia	Variable
Bronchial and salivary secretions	Sparse	Profuse	Variable
Gastrointestinal motility	Normal or decreased	Increased; diarrhea	Variable
Seizures	None	Common; focal or multifocal	Uncommon (excluding decerebration)
Electroencephalogram findings	Normal (awake)	Early: low-voltage continuous delta and theta. Later: periodic pattern (awake). Seizures: focal 1-to 1½-Hz spike-and-wave	Early: periodic pattern with isopotential phases. Later: totally isopotential
Duration	Less than 24 hr	Two to 14 days	Hours to weeks

The first change in stage 3 was further depression of the periodic pattern. The high-amplitude bursts decreased in frequency to every 6 to 12 seconds, and the low-amplitude intervals underwent further voltage depression to approach isopotential. A similar EEG pattern was seen during sleep in infants of stage 2 who had a periodic pattern in wakefulness. With progressive involvement in stage 3, the EEG became totally isopotential (Fig 3).

During recovery, the emergence from stage 2 was heralded by the reappearance of continuous cortical activity without periodicity in wakefulness. If recovery from stage 2 occurred within five days, the EEG reverted to normal (Fig 4). Later recoveries were characterized by a change from the periodic pattern to one of continuous low-amplitude delta and theta activity, similar to that seen on the first day in some infants. In recovering from a totally isopotential EEG, low-voltage delta and theta activity returned in wakefulness, but isopotential activity persisted in sleep during the same recording.

Focal motor seizures were characterized by 1- to 1½-Hz sharp and slow wave complexes of one hemisphere, usually in the central or temporal region (Fig 5). The focus sometimes shifted to the other hemisphere a few minutes later. Generalized paroxysmal activity and secondary bilateral synchrony were not seen. Clonus and movement artifacts were easily distinguished from true focal seizure activity (Fig 6).

Follow-up

Four severely affected infants died, and necropsy was performed in two (patients 1 and 2). In both cases, extensive encephalomalacia of the cerebrum and cerebellum was seen, with microcystic degeneration of cortical gray and subcortical white matter, extensive neuronal loss, and gross atrophy. No evidence of intracerebral or intraventricular hemorrhage was found, although minimal subarachnoid hemorrhage was present in the right parietal region of patient 2. Brain stem lesions were absent.

In an additional patient (No. 4), myoclonic epilepsy and hypsarrhythmia developed at 4 months of age, and he died at 11 months of age. Necropsy was not performed, but pneumoencephalography at 5 months of age showed extensive gyral atrophy, enlarged ventricles, and a widened subarachnoid space.

A bulging fontanelle or abnormal increase in the circumference of the head did not occur in any patient, either during the neonatal period or later.

A good outcome was seen in infants in whom the clinical signs of stage 2 and EEG reverted to normal within five days. The presence or absence of easily controlled seizure activity in the first two days did not seem to influence the prognosis. All infants who had normal development when seen at 6 to 12 months of age also had a normal EEG at that time.

The following features of the neonatal EEG appeared to be associated with a poor prognosis: (1) totally isopotential record at any time; (2) periodic pattern with an isopotential phase between bursts of activity that occurred less often than every six seconds, in wakefulness, obtundation, or stupor; (3) periodic pattern in wakefulness with continuous cortical activity between bursts that occurred every three to six seconds, but that persisted for seven days or more; (4) recovery from periodic pattern was to abnormal low-amplitude slow activity instead of to normal.

The results of this study thus suggest that the early prognosis of neonates suffering perinatal anoxic encephalopathy is good if they do not enter stage 3 and if the total duration of stage 2 is less than five days, followed by full recovery both clinically and electroencephalographically. The short-term follow-up precludes definitive conclusions about neurologic sequelae beyond the first year.

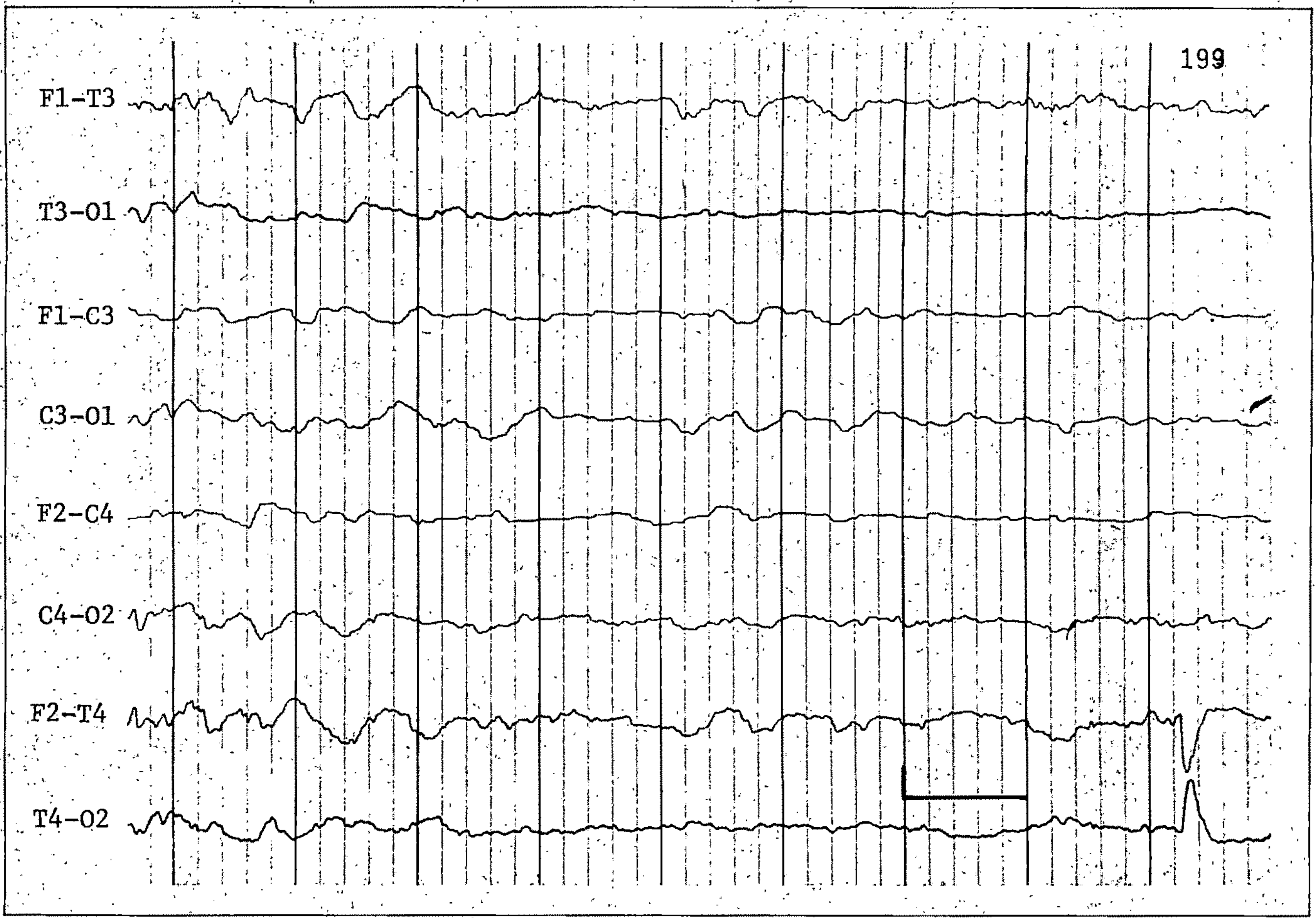
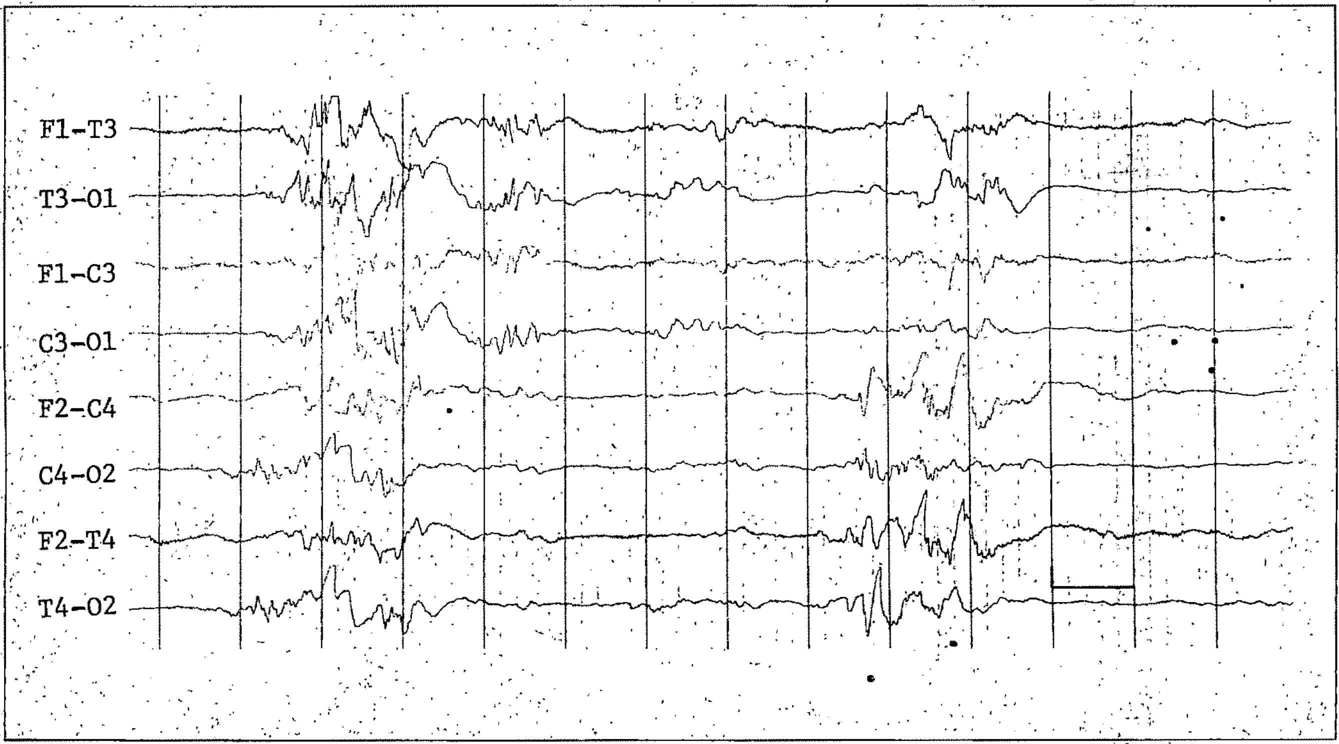


Fig 1.—Abnormal EEG during wakefulness showing generalized delta and theta slowing of low voltage, with paucity of faster theta and alpha range activity (compare with Fig 4). International 10-20 System of electrode placement. Calibration: 50μv, 1 second.

Fig 2.—Periodic EEG of patient 18 at 2 days of age while awake, during stage 2. High amplitude bursts occur simultaneously but not synchronously in two hemispheres. Calibration: 50μv, 1 second.



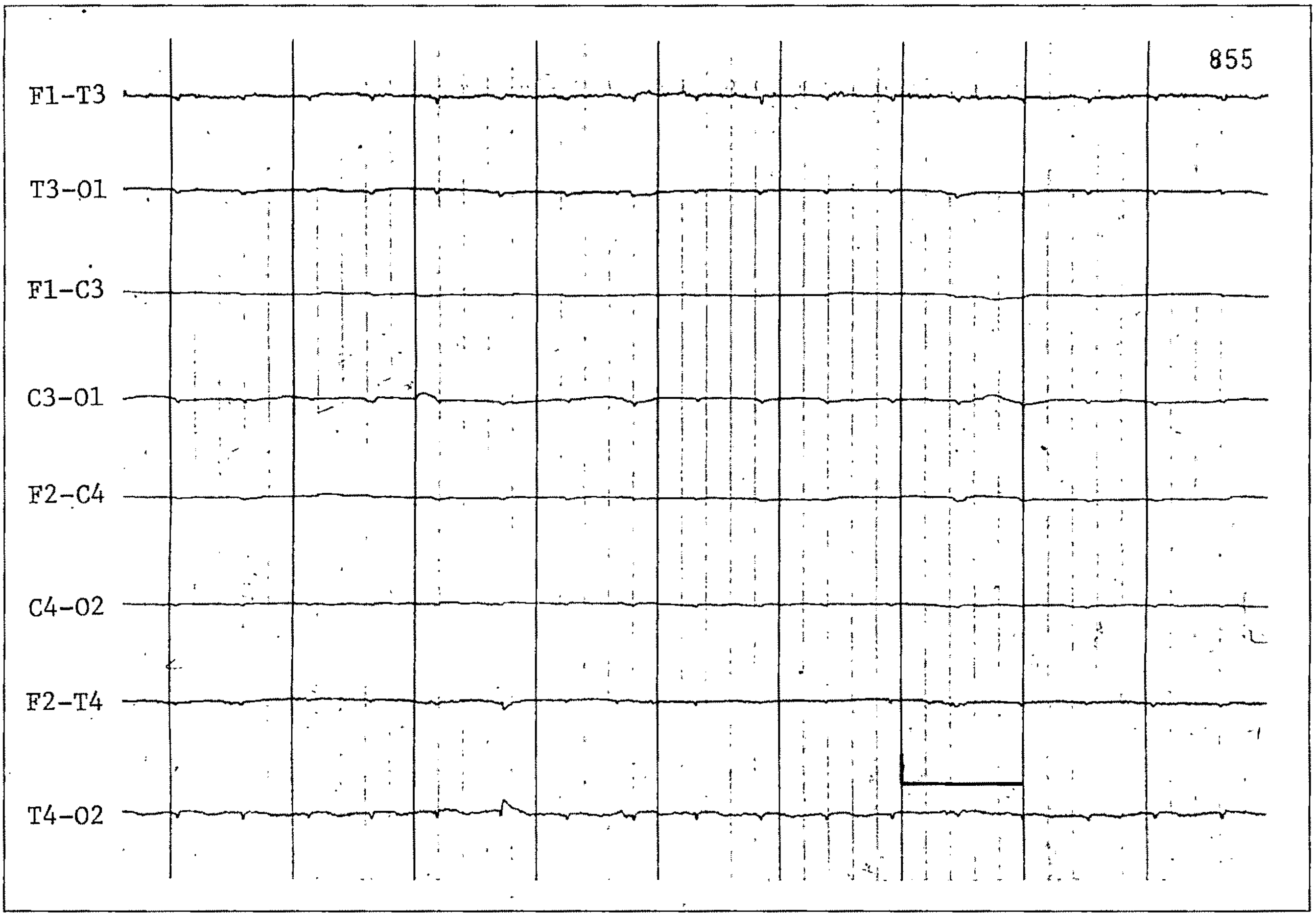


Fig 3.—Continuously isopotential EEG of stuporous infant at 5 days of age, during stage 3. Calibration: 50μv, 1 second.

COMMENT

None of the clinical or electroencephalographic characteristics here described are specific for postanoxic encephalopathy, but rather are manifestations of a state of functional impairment of the brain, especially the cerebral cortex, and also occur in other perinatal encephalopathies.

Many sympathomimetic manifestations of stage 1 may represent release of epinephrine by the adrenals rather than overactivity of sympathetic neurons or inhibition of the parasympathetic system. Plasma catecholamine levels rise dramatically in anoxic and postanoxic states in the newborn infant,[2,3] and the increase in circulating epinephrine may be as much as eightfold following placental insufficiency.[2] Hypoxia of mild degree (exposure to an atmosphere containing 10% oxygen for five minutes) in the postnatal period in full-term neonates did not result in increased urinary catecholamine excretion, however.[4] Hypoglycemia occurs commonly in postanoxic states in neonates,[5] and one third of infants in the present study had blood glucose concentrations of less than 40 mg/100 ml in the first few hours after birth, during clinical stage 1, or during early stage 2. Hypoglycemia does not decrease the epinephrine content of the adrenal medulla in newborn rats,[6] and it is likely that the hypoglycemia that follows perinatal asphyxia is secondary to high plasma epinephrine concentration, which causes depletion of hepatic glycogen reserves.

Most features of stage 2 suggest "release from inhibition" of brain stem and spinal cord reflexes and of vagal and other parasympathetic nerve function. This interpretation implies a selective vulnerability of brain stem inhibitory interneurons, of the cerebral cortex, or of both. An alternative explanation to parasympathetic overactivity is inhibition of the sympathetic system. Stage 3 is an extension of the process of progressive cephalocaudal neuronal depression throughout the neuraxis.

Because stage 1 is brief, severe fetal distress may result in signs of stage 2 or even stage 3 already at the time of delivery. Fetal tachycardia precedes bradycardia in the distressed fetus,[7-9] corresponding in utero to stages 1 and 2, respectively. Fetal monitoring also reveals that an early sign of loss of central nervous system control of the heart rate is the abolition of beat-to-beat irregularity.[7-9] The generalized parasympathetic discharge of stage 2 probably accounts for the passing of meconium stool into the amniotic fluid. Pinpoint pupils at birth, another parasympathetic sign, do not necessarily signify narcotic intoxication.

The respiratory pattern of asphyxiated neonates is incompletely characterized, but our observations suggest

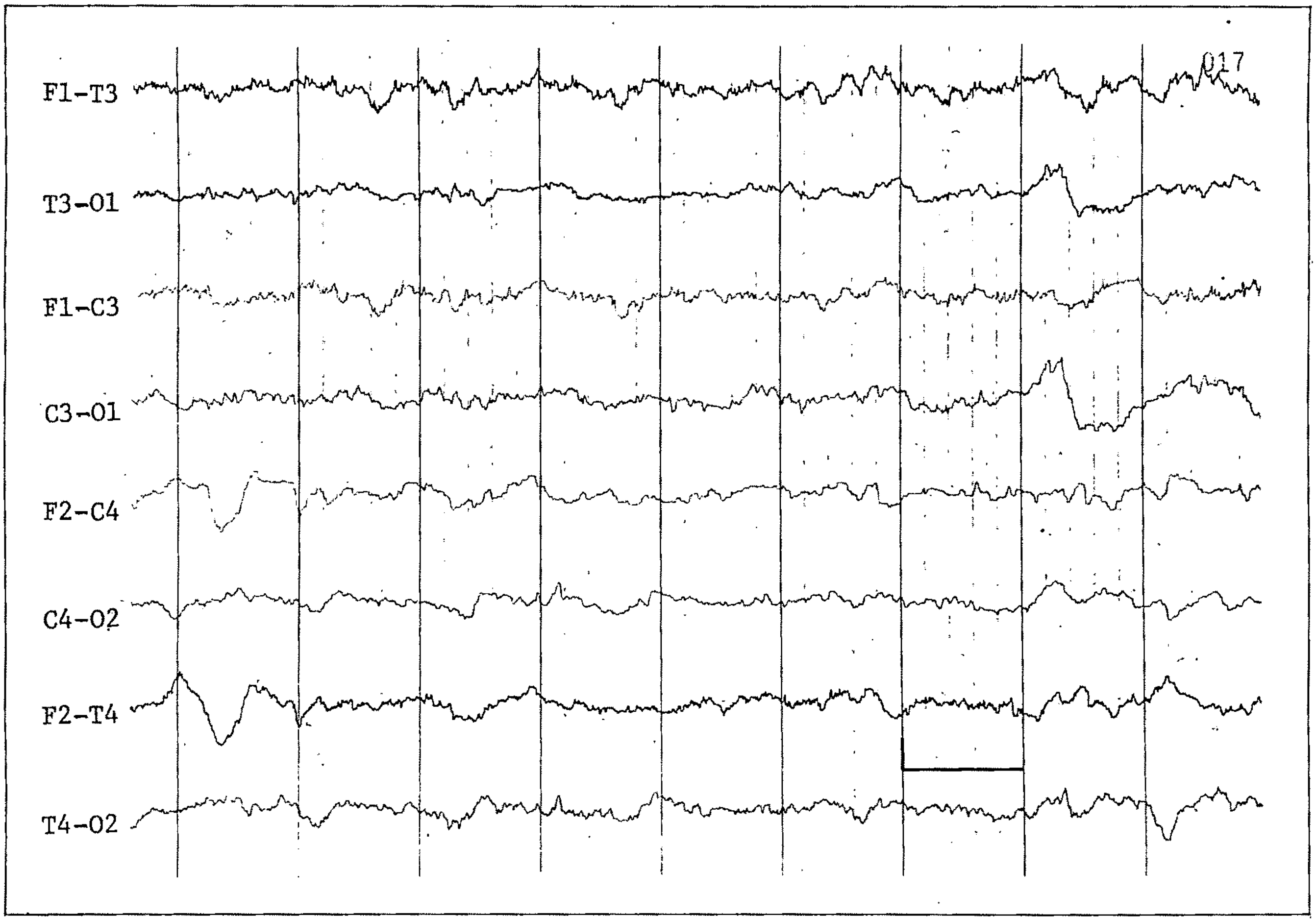
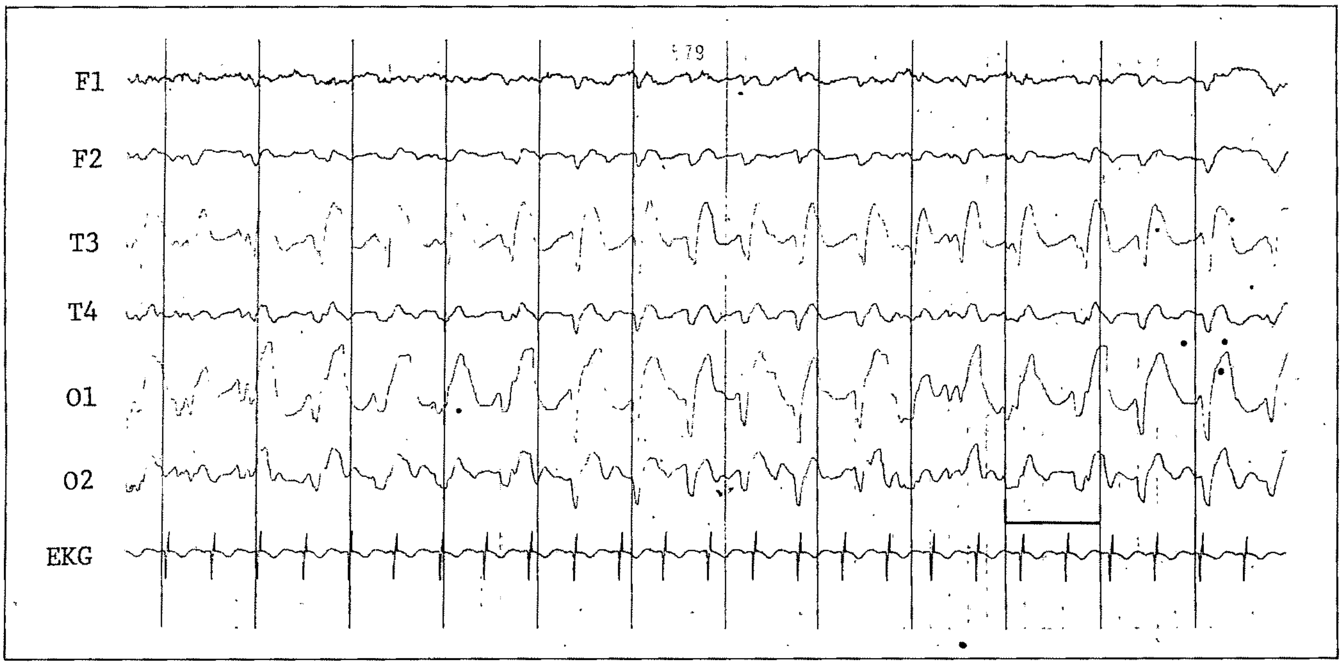


Fig 4.—Normal EEG of patient 18 at 6 days of age while awake, after recovering from stage 2 (same patient as Fig 2). Child now appears normal at 9 months of age. Calibration: 50μv, 1 second.

Fig 5.—Focal left temporo-occipital paroxysmal activity during right focal motor seizure. Characteristic 1- to 1½-hertz spike-and-wave complexes are seen at T3 and O1. Vertex (Cz) referential montage. Calibration: 50μv, 1 second. EKG indicates electrocardiogram.



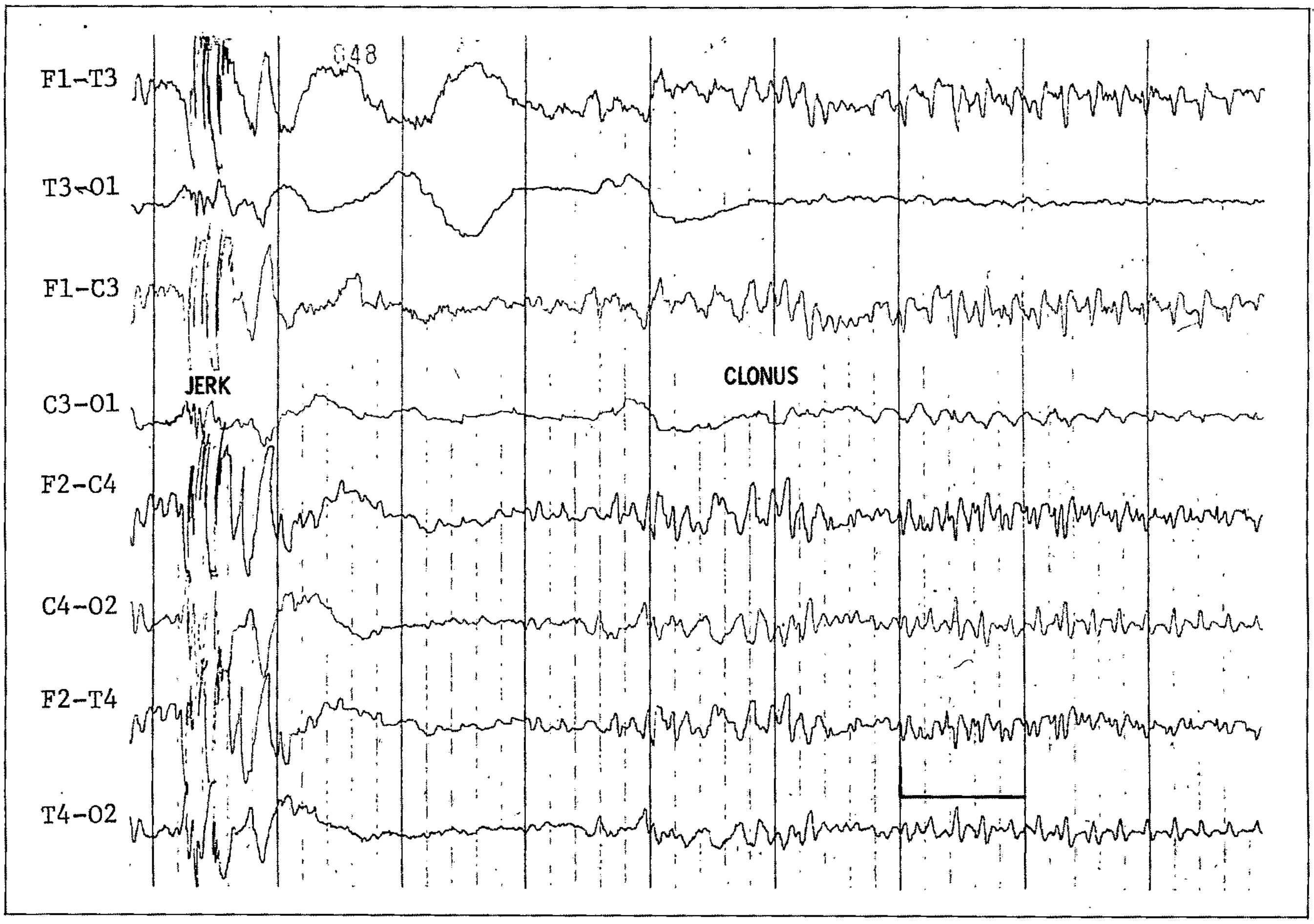


Fig 6.—Movement and clonus artifacts are distinguished from true seizure activity in neonatal EEG. Compare with Fig 5. Calibration: 50μv, 1 second.

that central neurogenic hyperventilation[1] and ataxic breathing[1] are common patterns. Apneic spells may alternate with periods of tachypnea. The breathing responses of fetal lambs are not affected by bilateral cervical vagotomy,[10] indicating that they are not under autonomic control. They are completely inhibited, however, by the maternal administration of pentobarbital and of quantities of thiopental sodium and methohexital sodium equal to or less than the doses used clinically.[10] These drugs depress cerebral activity in a manner similar to hypoxia.

The rhythmic tremor known as "jitteriness," "tremulousness," or "tremors" is a form of rhythmic segmental myoclonus and is found to a mild degree in normal full-term newborns when crying or excited. Clonus of the jaw is especially common. The segmental myoclonus of neonatal postanoxic encephalopathy is excessive and is unrelated to level of consciousness, since it may be seen in both stages 1 and 2 with hyperalertness and obtundation, respectively. The pathophysiology of this phenomenon involves more than simply release from inhibition of the segmental gamma loop of monosynaptic reflexes because it is not invariably associated with hyperreflexia and may involve such muscles as the orbicularis oculi as well as those of the extremities. The clinical distinction between segmental myoclonus and multifocal seizures in the newborn often is difficult to make by observation alone; taking hold of the clonic extremity and thus changing the tension on the muscle stretch receptors by slightly flexing or extending the joint immediately arrests clonus, but does not alter true seizure activity, during which rhythmic convulsive movements continue to be felt in the examiner's hand. The EEG also is useful in making this distinction (Fig 5 and 6). Neonatal segmental myoclonus does not respond to phenobarbital.

The semiperiodic EEG pattern in the postanoxic state has previously been observed in full-term neonates[11,12] and also in older children and adults.[13-16] It resembles the discontinuous EEG of premature infants of less than 30 weeks' gestation and the normal quiet sleep record ("tracé alternant") of normal 32- to 42-week neonates.[12,17-19] The pattern is nonspecific, and in full-term newborns often occurs as a postictal phenomenon. Postictal depression may even approach an isoelectric state, but seldom persists as such for more than 20 seconds.[12] Some authors regard the postanoxic periodic EEG pattern as a form of neonatal seizure activity.[20] We favor an alternative explanation: the periodic pattern represents impairment of intrinsic cortical rhythms (low-amplitude phase) and preservation of cortical responsiveness to direct activation from thalamic and brainstem centers (semiperiodic discharges).

The similarity of the periodic EEG pattern between neonates and adults in the postanoxic state suggests that the pathogenesis is not related exclusively to maturational factors. A similar periodic EEG is seen in normal premature infants, probably because of the immature state of synaptogenesis in the cortex. The third trimester of gestation is a time of active proliferation of cortical synapses, and coincides with a shift from a periodic EEG to one of continuous cortical activity during wakefulness. Neurons in the kitten cortex rarely exhibit spontaneous discharges in the immediate postnatal period,[21] probably because inhibitory synapses predominate at this stage of cortical development.[22] In asphyxiated full-term human infants, impairment of synapses or depletion of cortical neurotransmitters may cause the EEG to resemble that seen in the normal premature state of sparse synapse formation. Hypothermia also may play a role in potentiating the isopotential records seen in stage 3.[12]

The results of this study suggest that the quantitation of clinical and EEG data in terms of the duration of transitory findings during the first week after birth defines the severity of the insult to the brain and increases the accuracy of early prognosis in asphyxiated neonates. The persistence of abnormal EEG patterns after the second week in full-term infants already has been noted by Monod et al[23] to indicate a poor prognosis. In experimental hypoxia in fetal sheep, the time to recovery of normal EEG rhythms was a function of the length of the isoelectric stage, but not of the total period of hypoxia.[24]

On the basis of our findings of apparent tolerance of neonates to clincal and EEG features of stage 2 for five days without severe, irreversible brain damage, we recommend that at least two EEG records be made during the first week in asphyxiated infants, one on the second day and another on the sixth day after birth. Both wakefulness and sleep should be sampled. If still abnormal at 6 days of age, additional EEG recordings should be made every three or four days until it reverts to normal or shows no significant change by two weeks. The time course of the composite clinical and EEG changes provides a more sound basis for prognosis than do isolated symptoms and signs, the presence of seizures, or EEG changes alone.

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Hypothenar Dimpling

A Peripheral Equivalent of Hemifacial Spasm?

Saty Satya-Murti, MD, Robert B. Layzer, MD

• In two patients, the skin over both hypothenar eminences underwent intermittent, spontaneous, irregular, dimpling contractions. The dimpling was benign, and was the result of spontaneous discharge of motor units in the palmaris brevis muscle. Electrophysiological investigations localized the site of origin of the discharge to the ulnar nerve, possibly at the wrist, but there was no clinical or physiological evidence of neuropathy or of nerve compression. In many respects, the clinical and electrophysiological features of hypothenar dimpling resemble hemifacial spasm.

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We have recently encountered two patients with an unusual pattern of spontaneous dimpling in both hypothenar eminences, attributable to spasm of the palmaris brevis muscles. The dimpling was intermittent, longstanding, and unobtrusive. In fact, the symptom was merely a curiosity that the patients shared with their physicians. This rather unusual finding prompted us to investigate its nature with electrophysiological techniques.

REPORT OF CASES

CASE 1.—A 51-year-old housewife first became aware of "indentations" in her hypothenar eminences six years ago. These were never a source of discomfort, but kindled her curiosity. She had no other neurological symptoms, but in the course of her neurological evaluation it was discovered that she had mild, asymptomatic myotonia, without any family history of myotonia or myokymia. Percussion myotonia of the tongue was present. The skin over both hypothenar eminences underwent intermittent dimpling contractions producing linear horizontal creases (Fig 1). Contractions were more prominent in the left hand, and occurred more frequently when she was being examined. Sometimes hypothenar dimpling occurred in isolation; at other times it was accompanied by slight flexion of the little and ring fingers. Spasms began spontaneously and abruptly, lasting anywhere from a few seconds to more than two minutes. There was no other evidence of myotonia or spontaneous muscle contraction, and neurological examination was otherwise normal. Routine laboratory tests, including cervical spine roentgenograms were normal.

CASE 2.—A 67-year-old physician had noticed periodic, spontaneous contractions of the hypothenar eminences, especially the right, for three years. The spasms were not painful or intrusive in his daily activities, and he had no other neurological symptoms. The neurological examination was normal except for the dimples seen over the hypothenar eminences, especially the right. Slow, intermittent indentations occurred spontaneously, but the patient could produce a dimple at will by slight abduction of his little finger. After the abduction ceased, the dimple persisted for several seconds. No weakness, atrophy, or myotonia was seen anywhere. Except for diminished vibratory sensation in the feet, the remainder of the neurological examination was normal, and the results of routine laboratory tests were normal.

INVESTIGATIONS

Electromyography was performed using coaxial needle electrodes. Simultaneous paired recordings were obtained from the palmaris brevis muscle (PB) with each of the following muscles: abductor digiti minimi (ADM), adductor pollicis, flexor digitorum profundus (ulnar portion), flexor digiti minimi, first dorsal interosseus, flexor carpi ulnaris, and abductor pollicis brevis. The visible dimples were always associated with a high-

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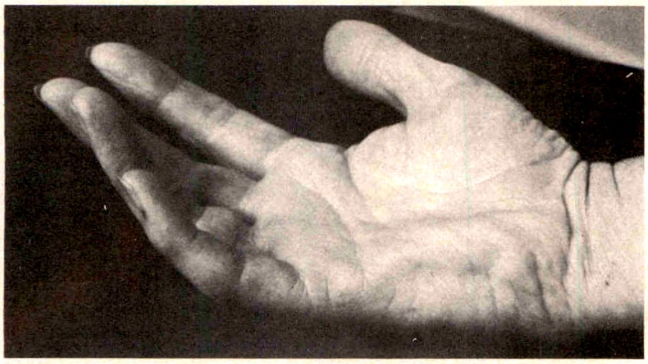

Fig 1.—Hypothenar dimpling in patient 1.

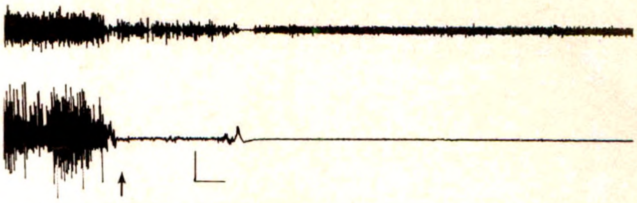

Fig 2.—Simultaneous electrograms from palmaris brevis (upper trace) and abductor digiti minimi (lower trace) in patient 2. After voluntary contraction of abductor digiti minimi stopped (arrow), discharge persisted in palmaris brevis. Calibration, 1 mV and 1 sec.

frequency discharge of the PB. Frequently, an interference pattern resulted, rendering it difficult to discern individual potentials. However, at times isolated potentials could be recorded. These had the configuration of normal motor units, with duration 5 to 9 msec and amplitude 0.6 to 0.8 mV. Three or more units were observed to discharge recurrently at frequencies between 1.5 and 13/second. The discharges occurred spontaneously, lasted anywhere from a few seconds to more than two minutes, and recurred at irregular intervals. In patient 1, the ADM also participated by firing occasionally for brief periods during the dimpling. Otherwise, in both patients all other intrinsic hand muscles or forearm muscles were electrically silent during the dimpling. In patient 2, brief voluntary contraction of the ADM could trigger the PB discharge, but the latter outlasted the brief ADM contraction by several seconds (Fig 2).

Motor conduction velocities and sensory latencies of the ulnar nerves and results of repetitive motor nerve stimulation were normal. Stimulation of the digital nerve of the fifth finger in patient 1 did not induce activity in the PB or modify a concurrent PB discharge. There was thus no evidence of an electrical connection between ulnar sensory and motor branches within the trunk of the ulnar nerve.

In patient 1, the ulnar nerve was infiltrated at the wrist with 2% lidocaine, resulting in complete nerve block, both electrically and clinically. This procedure totally abolished the dimpling and the PB discharges.

Comparison of Hypothenar Dimpling, Hemifacial Spasm, and Neuromyotonia

	Clinical Features	**Electromyographic Features**
Hypothenar dimpling	Focal, ulnar-innervated muscles, bilateral Benign, nonprogressive Irregular tonic contractions Aggravated by stress	Irregular discharges Initiated by abductor digiti minimi contraction in one case Normal units Abolished by nerve block
Hemifacial spasm	Focal, facial, usually unilateral Benign but embarrassing Irregular tonic and clonic contractions Aggravated by stress	Brief, high-frequency single unit discharges and prolonged irregular multiple unit discharges Probably normal units Abolished by nerve block
Neuromyotonia	Generalized, especially distal extremities Progressive, disabling Continual, waxing and waning ripples and stiffness Increased by voluntary contraction	Continual discharges Increased by voluntary contraction, with prolonged after-discharge Normal and fractionated units Diminished but not abolished by nerve block

COMMENT

The hypothenar spasms in these two patients were similar. The dimpling was spontaneous, irregular, bilateral, and asymmetrical, without stereotyped frequency or duration. The spasms had been present for several years without progression or annoyance. The contractions started and stopped with no apparent cause, although one patient could trigger them with voluntary abduction of the little finger. Otherwise, they could not be initiated at will. Rest and relaxation diminished or abolished them, while attention to them increased the contractions. Spontaneous muscle contractions were not present anywhere else in the body. There was no clinical evidence of ulnar neuropathy.

Electrophysiological studies revealed that the dimpling was caused by spontaneous contractions of the palmaris brevis muscle, accompanied by rapid discharge of motor units having normal amplitude, duration, and morphology. Occasionally, the ADM also discharged briefly with the PB in one patient, but none of the other muscles innervated by the ulnar nerve exhibited this type of activity. Nerve conduction tests gave no sign of ulnar nerve compression at the elbow or wrist. Block of the ulnar nerve at the wrist with lidocaine abolished the spontaneous discharges in the patient thus tested.

It is difficult to give a precise label to these movements. They lack the rippling, undulating appearance of myokymia. They do not resemble the single brief twitches of fasciculations. Although superficially they resemble the cases of neuromyotonia with myokymia described by Isaacs[1] and others,[2] there are several differences. Neuromyotonia is characterized by widespread muscle stiffness, myokymia, and delayed relaxation of voluntary contraction. The myokymic discharges wax and wane continually and consist of both normal and fragmentary motor unit potentials. Peripheral nerve block reduces but does not abolish the discharges. In contrast, hypothenar dimpling has remained localized to the same muscle for several years; the discharges consist of normal motor unit potentials and are abolished by nerve block.

On the other hand, hypothenar dimpling does resemble another entity characterized by involuntary contractions of muscles supplied by a single nerve, namely hemifacial spasm. Hemifacial spasm is a benign but troublesome disorder of adult life consisting of intermittent, irregular twitches of muscles innervated by the facial nerve.[3,4] Beginning in one muscle, such as the orbicularis oculi, the spasm may spread to other facial muscles, and can also be bilateral but asymmetrical in severity. Spasms vary from fine, localized twitches to vigorous, sustained contractions of one whole side of the face. The condition is aggravated by emotional stress. Although the cause is unknown, mechanical compression of the seventh cranial nerve in the cerebellopontine angle by a tortuous or elongated artery, an arteriovenous malformation, or a neoplasm has been identified in many cases.[5,6]

In the recent electromyographic study by Hjorth and Willison,[7] hemifacial spasm was associated with two types of discharges. One consisted of a brief, high-frequency repetitive discharge of the same motor unit; the other was a prolonged, irregular discharge of several units at lower frequencies (20 to 40/sec), often producing an interference pattern. The former was associated with brief, rapid twitches of the muscle, while the latter produced more prolonged, irregular spasms. Both types of discharge could often be provoked by voluntary blinking. A comparison of the clinical and electrophysiological features of hypothenar dimpling and hemifacial spasm is provided in the Table. The many similarities between these two conditions is apparent. It may be significant that both facial muscles and the PB are superficial muscles attached to the skin.

Since the discharges are so restricted, in all likelihood hypothenar spasms originate as spontaneous discharges from components of the ulnar nerve, usually only the branch to the PB. It is possible that a lesion of the ulnar nerve at the wrist is the basis of the disorder. The ulnar nerve divides into superficial and deep terminal branches as it passes into the wrist. The superficial branch supplies the PB muscle and sensation to the skin over the hypothenar eminence and palmar sufaces of the fourth and fifth fingers. The deep branch supplies all the other ulnar hand muscles. Since the PB is the major contributor to the dimpling, perhaps the ulnar nerve has been subjected to trauma or compression in the vicinity of its bifurcation into the deep and superficial terminal branches. The fact that blockade of the ulnar nerve at the wrist abolished the movements is consistent with this explanation. However, the proposed mechanism does not account for the occasional contribution of the ADM to the dimpling, nor does it explain why a conduction block was not found by electrical studies. Further, it is hard to understand why the disorder should be bilateral.

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Cell Volume and Permeability of Oxygen- and Glucose-Deprived Retina in Vitro

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• Rabbit retina was deprived of O_2 and glucose in vitro for up to four hours at 37 C. Intracellular volume was measured, using inulin as an extracellular marker. After a 30-minute latency, cells swelled rapidly to more than twice normal volume while extracellular volume was unchanged. Intracellular accumulation of water was not reversed by resupply of oxygen and glucose. Permeability to small molecules was assessed with mannitol. The ratio of mannitol space to inulin space averaged 1.0 in controls. This ratio remained 1.0 up to 30 minutes of deprivation, but increased to 1.2 by 60 minutes. Permeability to large molecules was assessed from the rate of loss of isotopically labeled cell protein into the medium. There was no difference between control and deprived retinas up to three hours.

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Cells subjected to ischemia undergo a progression of changes until a point is reached beyond which recovery is no longer possible. This study is concerned with two changes that may occur. One is increase in cell size, predictable from theoretical considerations[1] and previous experimental evidence (see "comment"). The other is an increase in cell permeability, suggested by the appearance of intracellular enzymes in blood of patients with infarctions.[2] Either of these changes might so interfere with cell function as to contribute to irreversible damage. An important objective of this study was to see if these changes occur early enough and are of sufficient magnitude to be possible causes of cell death.

The experiments were performed in vitro to permit control of the conditions to which cells were exposed, including introduction of a large extracellular marker (inulin) to measure cell volume and a smaller solute (mannitol) to test cell permeability. For evidence of more marked increases in permeability, the incubating medium was examined for intracellular proteins. The tissue employed was rabbit retina, an example of adult, mammalian central nervous tissue that is suitable for in vitro study. Ischemia was simulated by removing both O_2 and glucose from the incubating medium.

MATERIALS AND METHODS

New Zealand white rabbits were lightly sedated by intravenous administration of pentobarbital (10 mg/kg) and brought to surgical anesthesia with ether by mask. Retinas were isolated and incubated, as previously described.[3] All media were made to simulate cerebrospinal fluid in electrolyte composition, containing in milliequivalents per liter: Na^+, 143; K^+, 3.6; Ca^{++}, 2.3; Mg^{++}, 2.4; Cl^-, 125.4; HCO_3^-, 22.6; $H_2PO_4^-$, 0.1; $H_2PO_4^-$, 0.8; SO_4^-, 2.4. The control medium contained 10 mM glucose and was equilibrated with 5% CO_2 and 95% O_2. All retinas were preincubated in this medium for 30 minutes to permit recovery from the procedure of isolation and from the anesthetic. Both the ether and the barbiturate are promptly eluted from the tissue following immersion in the relatively large volume of medium (20 ml). Electrophysiologic studies of this preparation, performed from shortly after isolation until eight hours, have shown no residual effect of the anesthetics, even on integrated function such as demonstrated by directionally sensitive ganglion cells.[4] Some retinas served as controls and were permitted to remain in control medium for periods comparable to those used for test incubations. Test retinas were transferred for varying periods to the "deprivation medium," which was identical to the control medium except that it contained no glucose and was equilibrated with 5% CO_2 and 95% N_2. Some of the test retinas were returned to control medium for one or two hours to see if they could recover from the deprivation. All incubations were performed at 37 C in a volume of 20 ml per retina.

Ten minutes before the retina was removed for analysis, trace amounts of ^{3}H-inulin and ^{14}C-mannitol were added to the medium to label the extracellular fluid of the retina and to test membrane permeability. The ten-minute period for labeling was selected on the basis of previous studies[5] of the kinetics of inulin movement between medium and interstitial fluid. At the end of incubation, a retina was removed from the medium, touched three times to glass to drain off excess adherent medium, and cut from its optic nerve stump into a tared glass weighing vessel. Wet weights were determined immediately, and dry weights were determined after 16 hours under vacuum over P_2O_5. The retinas were extracted with 0.75M HNO_3 for 24 hours, and an aliquot of the extract was taken for differential counting in a liquid scintillation counter. Comparably small aliquots of medium, also diluted in 0.75M HNO_3, were similarly counted.

The total water in each retina was calculated as microliters per milligram of dry weight. From the counts per minute (cpm) of ^{3}H in the tissue and medium, the inulin "space" was calculated as microliters per milligram of dry weight from the following ratio: cpm ^{3}H per milligram dry weight retina/cpm ^{3}H per microliter of medium. Intracellular water, or inulin-free water, was then the difference between total water and inulin "space," also expressed as microliters per milligram of dry weight. The mannitol "space" was calculated from the following ratio: cpm ^{14}C per milligram dry weight retina/cpm ^{14}C per microliters of medium.

The appearance of intracellular proteins

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in the medium was measured in separate experiments to see if there was a more marked increase in permeability of plasma membranes. For these experiments, retinas were preincubated for two hours in control medium containing ^{3}H-leucine and enriched with the other amino acids and vitamins. On the basis of a previous study,[6] this would have resulted in a labeling of about 1% of tissue proteins. Retinas with their proteins thus labeled were then transferred to the deprivation medium or to the control medium, and the media were sampled periodically for the presence of labeled protein. The samples were centrifuged and 2 mg/ml serum albumin and 1 mg/ml unlabeled leucine were added to the supernatant. Aliquots were taken for counting before and after 10% trichloroacetic acid (TCA) precipitation. These counts served to measure, respectively, total ^{3}H-leucine and free ^{3}H-leucine. The protein-incorporated ^{3}H leucine was determined from the difference.

RESULTS

Cell Swelling

Figure 1 shows the change in total tissue water as a function of incubation time, both in control medium and in deprivation medium. The total water of retinas incubated in control medium remained quite constant throughout the 180-minute period studied. Retinas incubated in deprivation medium showed marked increases in total water between 30 and 60 minutes, with a continued, slower increase thereafter. Figure 2 shows the change in inulin-free water, or intracellular water, as a function of time of incubation under the two conditions. Control retinas showed no progressive change in intracellular water during the 150-minute incubation. Retinas deprived of O_2 and glucose also showed no change for the first 30 minutes; however, between 30 and 60 minutes they almost doubled their intracellular volume, with a continued slower increase thereafter. It is apparent from the data that the increase in total water with depriva-

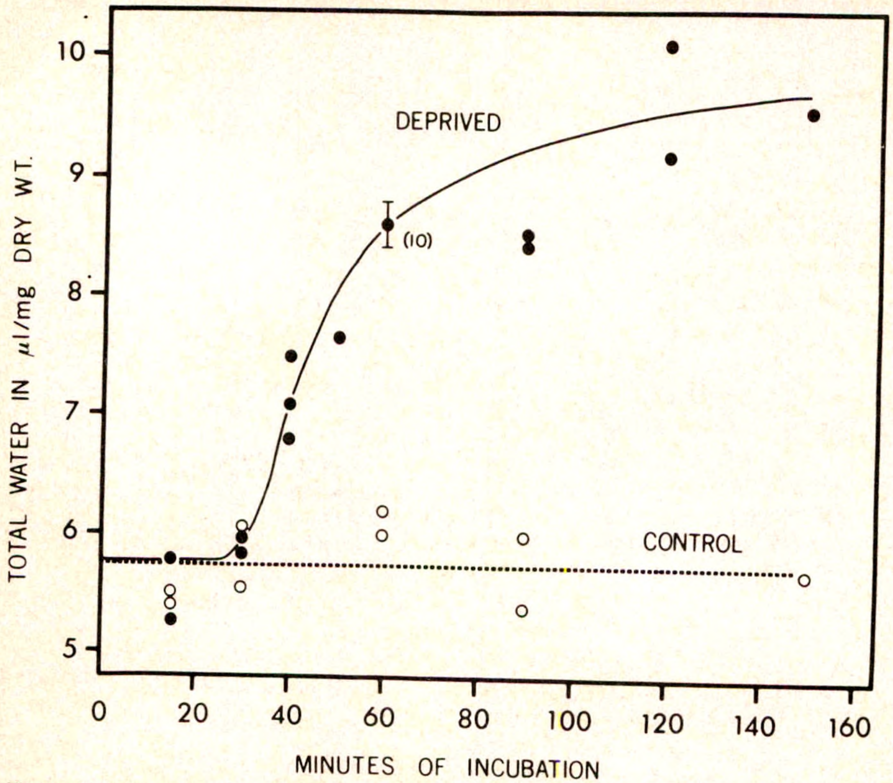

Fig 1.—Total tissue water after incubations under control conditions (open circles) and after incubations without O_2 or glucose (solid circles). Broken line indicates mean of all controls. Solid line fitted by eye to data on deprived retinas. Vertical bar indicates standard error of the mean; number of retinas in parentheses.

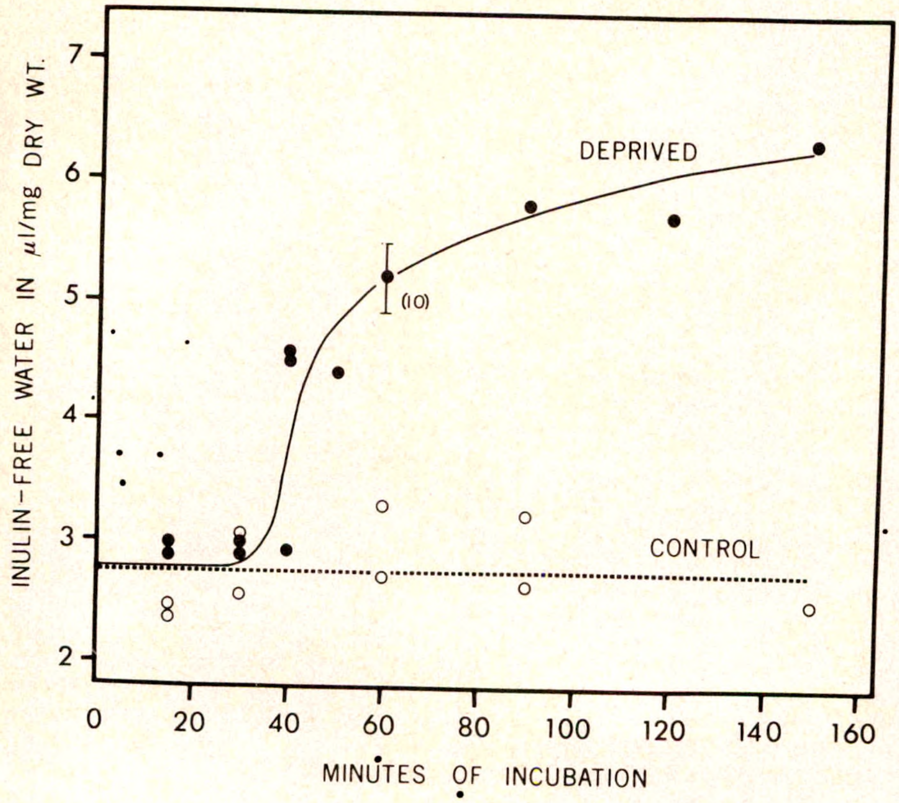

Fig 2.—Inulin-free water after incubations under control conditions (open circles) and after incubations without O_2 or glucose (solid circles). Broken line indicates mean of all controls. Solid line fitted by eye to data on deprived retinas. Vertical bar indicates standard error of the mean; number of retinas in parentheses.

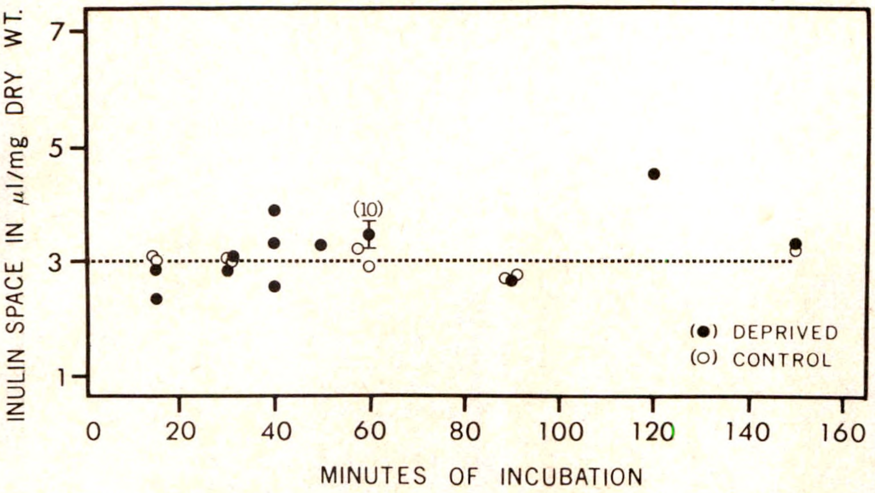

Fig 3.—Inulin space, after incubations under control conditions (open circles) and after incubations without O_2 or glucose (solid circles). Broken line indicates mean of all controls. Vertical bar indicates standard error of the mean; number of retinas in parentheses.

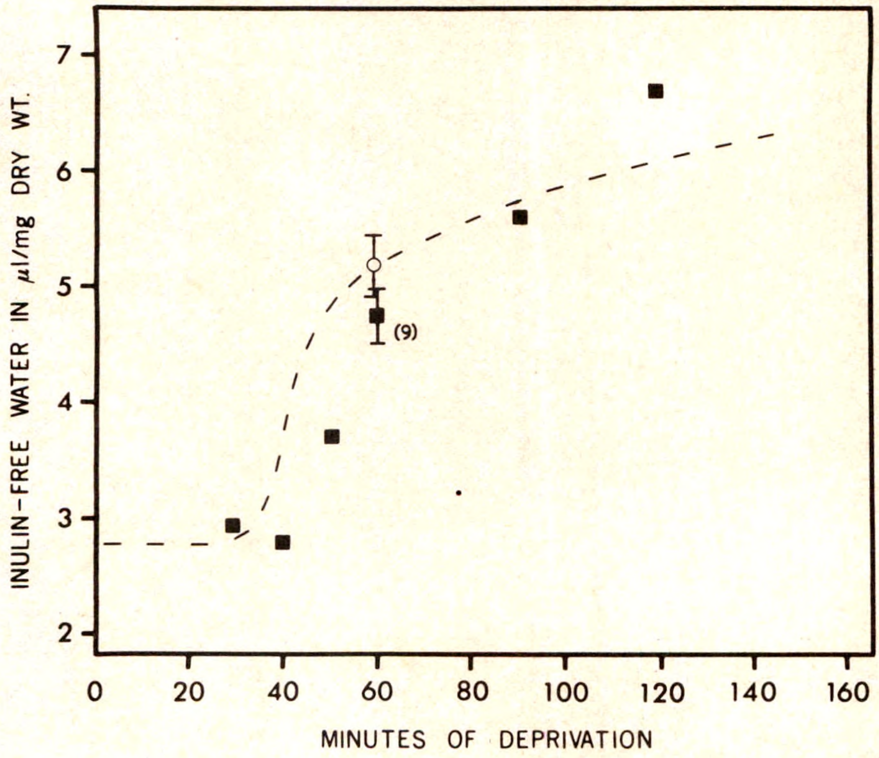

Fig 4.—Inulin-free water after resupply (one or two hours) of O_2 and glucose (solid squares), plotted as a function of length of deprivation. Curve (broken line) of data from retinas deprived without resupply, reproduced from Fig 2 for comparison. Vertical bars indicate standard errors of the means; number of retinas in parentheses.

tion (Fig 1) is ascribable to an increase in intracellular water (Fig 2), and that there was no appreciable change with deprivation in the size of the extracellular space. This is shown more directly in Fig 3, where inulin space has been plotted as a function of deprivation time.

In experiments to test reversibility of deprivation-induced swelling, retinas deprived of O_2 and glucose for varying periods were returned to control medium for one or two hours of resupply. Their intracellular volumes were compared with those of controls and of retinas deprived for the same periods but with no resupply. As shown in Fig 4, retinas deprived for 30 to 40 minutes continued to maintain a normal intracellular volume during the subsequent one-hour resupply. Retinas deprived for more than 60 minutes either did not improve or appeared to swell further during the period of resupply. Ten retinas were deprived for 60 minutes without resupply and nine retinas were deprived for the same period but were then returned to control medium for two hours. The mean values for intracellular water of these two groups have been plotted in Fig 4 with bars to indicate their standard errors. The difference between the two conditions was not significant.

Change in Permeability of Plasma Membranes

A marked increase in the permeability of the plasma membranes would have permitted inulin to enter cells freely so that its volume of distribution would have approached the volume of total tissue water. This was not observed. As shown in Fig 3, the inulin space did not increase during 150 minutes of deprivation. The size of the inulin space, however, is a relatively insensitive indicator for increased permeability, since inulin is a fairly large molecule (molecular weight about 5,000). Mannitol is much smaller (molecular weight, 182), and its volume of distribution did increase after 50 minutes of deprivation. The ratio of mannitol space to inulin space is a more sensitive index of a change in mannitol permeability than the mannitol space itself, since this ratio is insensitive to possible variations in the volume of interstitial fluid and adherent medium. As shown in Fig 5, this ratio did not differ significantly ($P = .7$) from 1 for control retinas or for retinas deprived up to at least 30 minutes. However, by 60-minute deprivation, it had increased significantly ($P < .001$) to an average of 1.2 and apparently increased further thereafter. In retinas returned to control medium after deprivations up to 50 minutes, the ratio remained normal. Resupply after longer deprivations not only failed to restore the ratio, but led to further increases.

Rate of Appearance in Medium of Label Incorporated Into Protein

Some retinas were preincubated with ^{3}H-leucine to label their intracellular proteins. Rupture of cells during deprivation, or a very great increase in their permeability, would have led to appearance of proteins in the medium. Examination of media for TCA-insoluble label revealed less than one half of 1% per hour of labeled proteins appearing during the first three hours of incubation in either control or deprivation medium (Fig 6). After three hours, there was visible fragmentation of deprived retinas. Deprivation also had no marked effect on appearance of TCA-soluble label, indicating that proteolysis secondary to lysosomal or other proteolytic activity had not been a prominent feature of the response to deprivation. Enzymatic studies by Clendenon et al[7] and quantitative morphologic studies by Shay[8] on ischemic central nervous tissue have led to a similar conclusion.

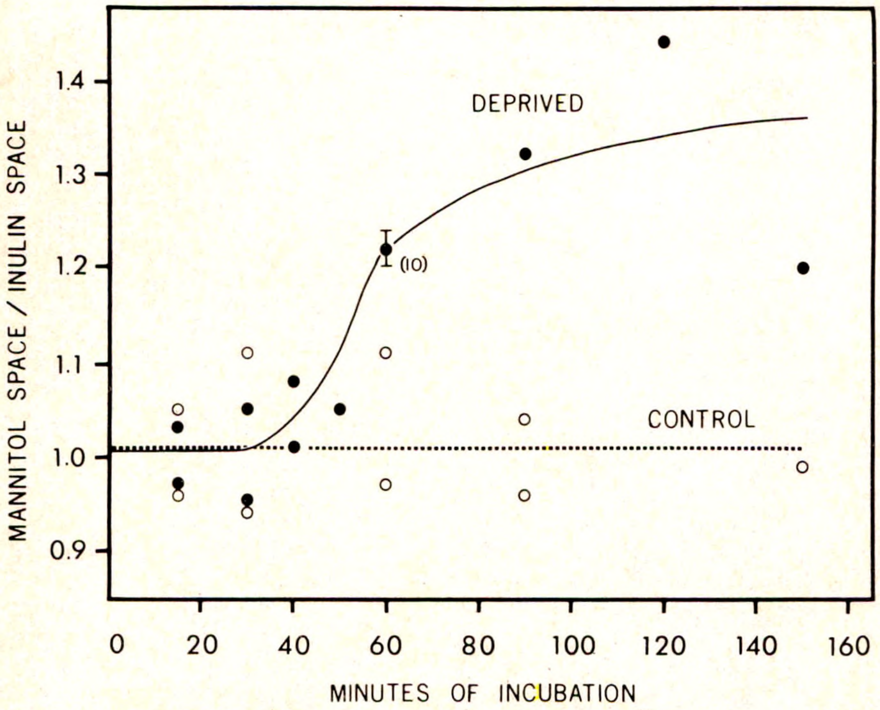

Fig 5.—Ratio of mannitol space/inulin space after incubations under control conditions (open circles) and after incubations without O$_2$ or glucose (solid circles). Broken line indicates mean of all controls. Solid line fitted by eye to data on deprived retinas. Vertical bar indicates standard error of the mean; number of retinas in parentheses.

COMMENT

Cell Swelling

When deprivation of O$_2$ and glucose lasted more than 30 minutes, there was a progressive increase in tissue water, and since the added water was not accessible to inulin, it seems reasonable to conclude that it represented an increase in intracellular volume. This conclusion is supported by a histological study of retinas similarly treated (see p 715). An increase in water, as a consequence of deprivation of oxygen or substrate or both, has been observed in other in vitro preparations. *Brain slices* have shown an increase in total water when deprived of oxygen,[9-12] glucose,[10-13] or both.[14] When inulin was used as an extracellular label, this increase was demonstrated to have occurred primarily in the intracellular compartment.[11,13,14] *Kidney slices* have shown

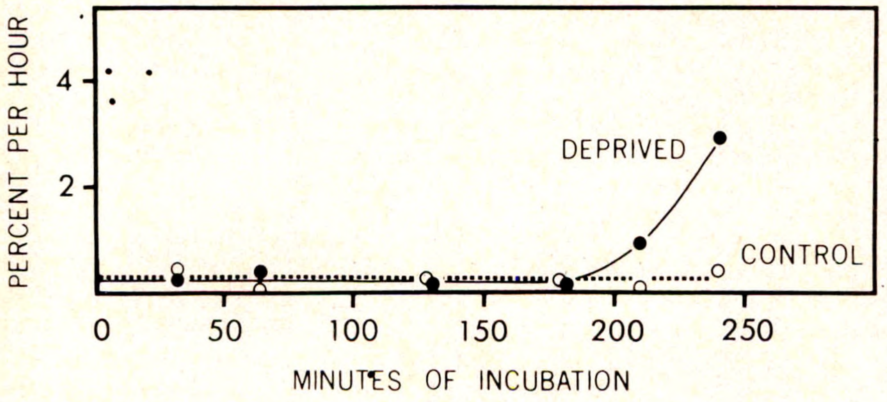

Fig 6.—Labeled protein appearing in medium during incubations under control conditions (open circles) and during incubations without O$_2$ or glucose (solid circles). Rate at which trichloroacetic acid-insoluble ^{3}H appeared in medium has been plotted as percent per hour of the initial ^{3}H in cell protein. (Proteins had been labeled with ^{3}H-leucine during a prior incubation in medium containing O$_2$ and glucose; see text). Broken line indicates mean of all controls. Solid line fitted by eye to data on deprived retinas.

an increase in total water during incubation without oxygen,[12,15-17] and similar findings have been reported for *liver, lung,* and *spleen.*[12] In studies performed in vivo, 30 to 60 minutes of circulatory arrest led to an appreciable increase in the water content of papillary muscle[18,19] and brain.[20-22] This was manifested shortly after restoration of flow, except in the case of the superficial layers of the cerebral cortex, which had direct access to the CSF and whose volume increased 20% during the ischemia.[20,21]

The mechanism responsible for the cell swelling is not well understood. Water moves readily across plasma membranes to maintain osmotic equilibrium.[23,24] In our experiments, as in those previously cited, extracellular osmolarity remained quite constant, so that the increase in cell volume during ischemia must reflect an increase in intracellular solutes. There might be an increase in organic solutes within cells if ischemia leads to net accumulation of catabolic products that do not readily pass the plasma membrane. There is, however, little evidence for this when both O_2 and substrate are withheld, and there is some evidence to the contrary.[18] A more likely explanation is an increase in the sum of intracellular inorganic electrolytes. An increase in electrolytes has been predicted as a consequence of failure of active transport[1] and has been demonstrated experimentally.[1,25] However, in some preparations of liver and kidney poisoned with ouabain, swelling failed to occur, despite considerable loss of cell K^+ and gain of Na^+.[26] Net shifts of electrolytes would be facilitated if the plasma membrane became more permeable as a consequence of energy deprivation. That this may have been a factor in the present experiment is suggested by the increased permeability to mannitol. The long time interval between beginning of deprivation and onset of swelling in our experiments remains unexplained. It may reflect the time required for failure of active transport or for a change in electrolyte permeability of the retina.

Cell swelling resulting from 60-minute deprivation appeared to be irreversible when O_2 and glucose were resupplied to the tissue. It is possible that reversal of swelling could be demonstrated with retinas deprived somewhat less than 60 minutes, which was the period we most intensively studied. It is also possible that reversal of swelling of some cells during resupply was obscured by continued swelling of others. We have found few published studies on the reversibility of cell swelling induced by deprivation of oxygen and/or glucose in vitro at 37 C. Whittam and Davies[17] have reported that kidney slices resupplied with O_2 after 15 minutes of anoxia had normal tissue water, but no data were presented on the effects of 15 minutes without oxygen, so it is unclear whether swelling had occurred in the first place. Robinson[16] found that swelling of kidney slices, induced by cyanide, could be reversed if the cyanide was removed.

Permeability Changes

In control retinas, the volume of mannitol distribution approximately equaled the volume of inulin distribution. In a previous study performed under control conditions,[5] the volume of mannitol distribution corresponded not only to the volume of inulin distribution but also to the volume occupied by the readily elutable fractions of Na^+ and Cl^-. Thus, the mannitol space appears to correspond to the extracellular fluid in retinas incubated under control conditions. However, after 30 or 40 minutes of O_2 and glucose deprivation, the mannitol space increased in absolute terms and increased relative to the inulin space. It seems reasonable to conclude that this represented penetration of mannitol into the cells. This increased permeability to mannitol may have been due to mechanical stretching of the plasma membranes as a consequence of the cell swelling or due to an ischemia-induced change in the structural components of the membranes. Some evidence for the latter is the rapid increase in ischemic brain of free fatty acids, whose source appears to be membrane phospholipids.[27] The plasma membranes remained impermeable to much larger molecules for considerably longer, as evidenced by the absence of change in inulin space for up to 150 minutes, and the effective retention of intracellular proteins until after 180 minutes of deprivation.

There have been few studies of changes in permeability to small molecules during oxygen and/or glucose deprivation. Page et al[25] found that the mannitol space had increased in cat ventricular papillary muscle after three hours of incubation without O_2. Piccoli and Lajtha[28] found that mannitol penetration of the inulin-free space of brain slices was increased by cyanide. More extensive documentation is available for the marked changes in plasma membranes that appear later in the course of an ischemic insult. These changes lead to the appearance in plasma of intracellular enzymes, measurement of which has proven useful in clinical diagnosis of infarction.[2]

It is remarkable that retinal cells were able to more than double their intracellular water without evidence of loss of protein or entry of inulin. In ten retinas deprived of O_2 and glucose for 60 minutes, the inulin-free water averaged 191% of normal, and in three retinas deprived for 90 to 150 minutes, it averaged 216% of normal. However, there was no evidence that abnormal quantities of intracellular protein were released into the medium until after 180 minutes of deprivation. Studies on red blood cells in hypotonic media have shown that their plasma membranes tolerate little stretching before they become freely permeable to hemoglobin.[29] It is possible that retinal cells, almost all of which have extended processes, underwent reshaping to encompass a much larger volume within the same area of membrane. If this occurred, it is not unreasonable to expect that it would seriously threaten continued normal function of the cells. Another possibility is that intracellular membranes became incorporated into plasma membrane.[30]

Relation of These Changes to the Point of Irreversible Damage

In retinas resupplied with O_2 and glucose after 30 minutes of deprivation, the cells continued to maintain their normal size and permeability. However, retinas resupplied after 60 minutes of deprivation showed little evidence of recovery from their swelling and increased permeability to mannitol. Thus, by these two criteria, the time required for irreversible damage of a large portion of the cells lay between 30 and 60 minutes. Other criteria have led to the same conclusion. Retinas failed to recover normal physiological function after 30 minutes of O_2 and glucose deprivation.[31] They showed early, irreversible changes in structure after 30 or 40 minutes[3] (also see p 715), and the irreversible structural damage was quite general by 70 minutes (see p 715). Protein synthesis was markedly diminished in retinas that had been subjected to 60-minute deprivation and then exposed to labeled leucine after two hours of resupply (J. M. Parks, PhD, unpublished data).

These findings indicate that the onset of irreversible damage for many cells occurs between 30 and 60 minutes of O_2 and glucose deprivation, or at about the time that the cells are undergoing marked swelling and becoming permeable to mannitol. It is therefore possible that either the swelling or the permeability change is directly related to the cells' death. On the other hand, both of these changes may represent early postmortem phenomena or may be occurring in parallel with other changes that are responsible for the failure to recover.

Relevance to Ischemia in Vivo

In the in vitro experiments described here, the primary variable was removal of O_2 and glucose. Circulatory arrest also results in loss of O_2 and of glucose, but these are not the only changes that occur. Circulating blood normally maintains the composition of interstitial fluid quite constant and in effect provides an infinite reservoir that serves both as source and sink for substances moving in and out of cells. When flow stops, a closed system is created so that cells can exchange only with the interstitial fluid. The first effect of this would be changes in concentration of those substances that exhibit the largest net fluxes across the plasma membrane, ie, O_2, glucose, and CO_2. However, the resulting impairment of energy metabolism can be expected to upset the normal steady state and to result in net movements of other solutes and of water. Since the interstitial fluid volume is small, net fluxes would lead to changes in its composition (eg, rise in K^+, fall in Na^+ and Ca^{++}). The present experiments did not duplicate these changes. As shown in the article by Shay and Ames (see p 715), for neurons they may be of minor importance compared with primary interruption of energy metabolism, but limitation of volume of exchange appears to be particularly detrimental to astroglial cells.

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Retina Subjected to Components of Ischemia In Vitro

Selective Vulnerability and Minimum Lethal Exposure of Neurons and Glia to Oxygen and/or Glucose Deprivation and to Loss of Exchange With Incubating Medium

Jonathan Shay, MD, PhD, Adelbert Ames III, MD

• Rabbit retinas were incubated at 37 C in media lacking oxygen, glucose, or both, or sealed in a small compartment without medium to convert them to a "closed system." They were then returned to control medium before being fixed for microscopy. Other retinas were incubated only in control medium and then fixed. Conversion of the retina to a closed system caused irreversible damage to all cell types within 40 minutes. Combined deprivation of oxygen and glucose also irreversibly damaged the neuronal cells within 40 minutes, but Mueller cells, the principal glial cells of the retina, were not irreversibly altered by 90 minutes of the deprivation. Deprivation of oxygen alone caused irreversible damage to receptor cells in 80 minutes, but the cells of the inner nuclear layer, ganglion cells, and Mueller cells retained normal structure for at least 180 minutes. Deprivation of glucose alone damaged receptor cells in 160 minutes and the other neuronal cells in 180 minutes, but did not irreversibly damage Mueller cells by 200 minutes.

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Cessation of blood flow alters the external environment of cells in a number of ways, several of which have been implicated as the cause of irreversible damage. The lack of oxygen, the lack of glucose, and other alterations of the composition of the extracellular fluid that occur after blood flow stops are difficult, if not impossible, to separate experimentally from one another in the intact animal.[1] The isolated rabbit retina offers an opportunity to study some of these factors separately, as they affect the survival of central nervous tissue. We have assessed the selective vulnerability of the different cell types of the retina to different features of the ischemic insult in order to obtain "baseline" data for further investigations into mechanisms of damage to specific cell types in the central nervous system (CNS).

The retinas were incubated for varying periods in media lacking oxygen, glucose, or both, or they were removed altogether from contact with medium and gas exchange to reproduce more faithfully the conditions during circulatory arrest in vivo. Our objective was to determine the times of onset of *irreversible* damage. Therefore, we returned all test retinas to control medium for one or more hours before examining them with the light microscope for the presence or absence of cell structural differences from controls. Structural abnormalities that were still present after a period of restored normal conditions were taken as evidence of the cells' inability to recover.

MATERIALS AND METHODS

Retinas were isolated from the eyes of New Zealand White rabbits, according to procedures previously reported.[2] The interval between interruption of the circulation and immersion of the hemisected eye (with its vitreous removed) in fresh incubating medium was never longer than one minute and was usually less than 30 seconds. After isolation, all retinas were preincubated in control medium, which was gassed with 95% O_2/5% CO_2 at a rate of 50 ml/min. The composition of the control medium was as follows.

Milliequivalents per Liter of Solution

NA^+	143.0	Cl^-	125.4
K^+	3.6	HCO_3^-	22.6
Ca^{2+}	2.3	$H_2PO_4^-$	0.1
Mg^{2+}	2.4	HPO_4^{2-}	0.8
Total	**151.3**	SO_4^{2-}	2.4
Total			**151.3**

Milliosmols per Liter of Solution

Electrolytes	298.7
Glucose	10.0
Total	**308.7**

Control retinas remained in control medium for periods ranging from 5 to 300 minutes, and were then fixed for microscopy. Other retinas were preincubated in control medium for 30 minutes and then exposed to one of the deprivation condi-

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tions for a given period of time. They were then returned to control medium for at least one hour. All incubations were conducted at 37 C.

Conditions of Deprivation

Four conditions of deprivation were employed (Fig 1).

1. Closed System Deprivation.—Retina was sealed in an empty $400 \mu l$ Teflon chamber under 95% N_2/5% CO_2 to convert it to a "closed system," in which the cells were deprived of exchange with fluid beyond the confines of the tissue.

2. Combined Oxygen and Glucose Deprivation.—The retina was incubated in 20 ml of medium identical to control, except that it contained no glucose and was gassed with 95% N_2/5% CO_2 at a rate of 50 ml/min.

3. Oxygen Deprivation.—Retina was incubated in medium containing 10 mM glucose but gassed with 95% N_2/5% CO_2, as previously mentioned.

4. Glucose Deprivation.—Retina was incubated in 20 ml of medium containing no glucose but gassed with 95% O_2/5% CO_2.

Table 1 shows the number of retinas studied, according to kind and length of deprivation. All deprived retinas were resupplied with oxygen and glucose for one hour in control medium, with the exception of four oxygen- and glucose-deprived retinas that were resupplied for four hours. Retinas were fixed for one hour in an iced solution consisting of 1% osmic acid in the control incubating medium. It has been shown previously[3] that fixation of retina in this manner preserves relative size changes of cellular structures under conditions of osmotic swelling and shrinkage. The retinas were dehydrated in ascending ethyl alcohols and propylene oxide, passed through 50/50 mixture of propylene oxide and Epon, and then infiltrated with Epon. They were stained overnight in block during the 50% ethanol dehydration step with saturated uranyl acetate. After mincing with a razor blade, ten small pieces of retina selected at random were oriented in a drop of Epon in flat embedding molds, with an edge toward the tip of the mold. After curing, four blocks were chosen at random for 1μ sections that were stained with toluidine blue.

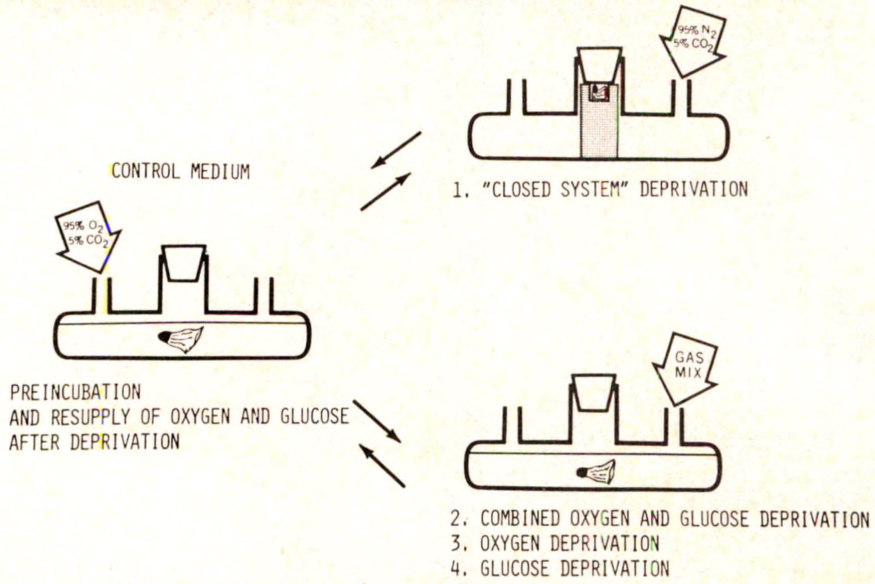

Fig 1.—Incubating conditions and sequence. After isolation from eyes, all retinas were "preincubated" in control medium. Control retinas remained in control medium and were then fixed. Test retinas were shifted from control medium to one of four conditions of deprivation for a given period of time and then returned to control medium for resupply of oxygen and glucose. All test retinas were fixed after resupply for study of residual structural damage that had not been reversed by resupply of oxygen and glucose. (See text for details.)

RESULTS

As reported previously,[2] control retina morphologic findings did not differ significantly from retinas fixed in situ. In this study, control incubations of longer than 15 to 30 minutes resulted in appearance of numerous extracellular spaces in the inner nuclear layer (Fig 2). Such spaces were unstained and contained neither nuclei nor debris, and were thus easily distinguished from swollen cells. Beyond 30 minutes, these spaces did not increase as a function of time of incubation. In other studies performed under the same conditions, there were no significant changes in the functional capacity of the incubated retina, as indicated by continued maintenance for at least six hours of normal electrophysiologic response to photic stimuli,[4] normal intracellular electrolytes,[5,6] and a normal rate of protein synthesis.[7] By these functional criteria, the retinas are well maintained under control conditions for many hours in vitro. Similar spaces in the inner nuclear layer are seen in retinas that have otherwise completely recovered from deprivation. Since they were invariably observed in control retinas incubated a comparable total period, we believe they should not be viewed as a consequence of deprivation. Similarly, occasional ragged extracellular spaces were encountered in the inner plexiform layer, particularly on prolonged incubation. Scattered individual swollen or pyknotic cells were rarely (<5 per 1,000 cells) observed in controls.

Selective Vulnerability of Retinal Cells Following Prolonged Exposure to the Different Insults

In an attempt to show gross differences in vulnerability between retinal cell types to different kinds of deprivation, we subjected retinas to prolonged periods of deprivation. Compared with controls, 90 minutes of closed system deprivation (Fig 3, top left) resulted in structural changes not reversed by resupply to all cell types in the retina. All neurons, with exception of some pyknotic ganglion cells, were swollen. Mueller cell (astroglial) cytoplasm appeared coagulated and nuclear chromatin appeared clumped. What appeared to be remnants of extensive swelling (blebbing) of the Mueller cell beyond the inner limiting membrane was noted. By contrast (Fig 3, top right), 90 minutes of combined oxygen and glucose deprivation resulted in marked irreversible structure change of all the neurons in the retina, but Mueller astroglial cells retained normal structure. This contrast between the selective vulnerability of Mueller cells in closed system and simple combined oxygen and glucose deprivation is shown more

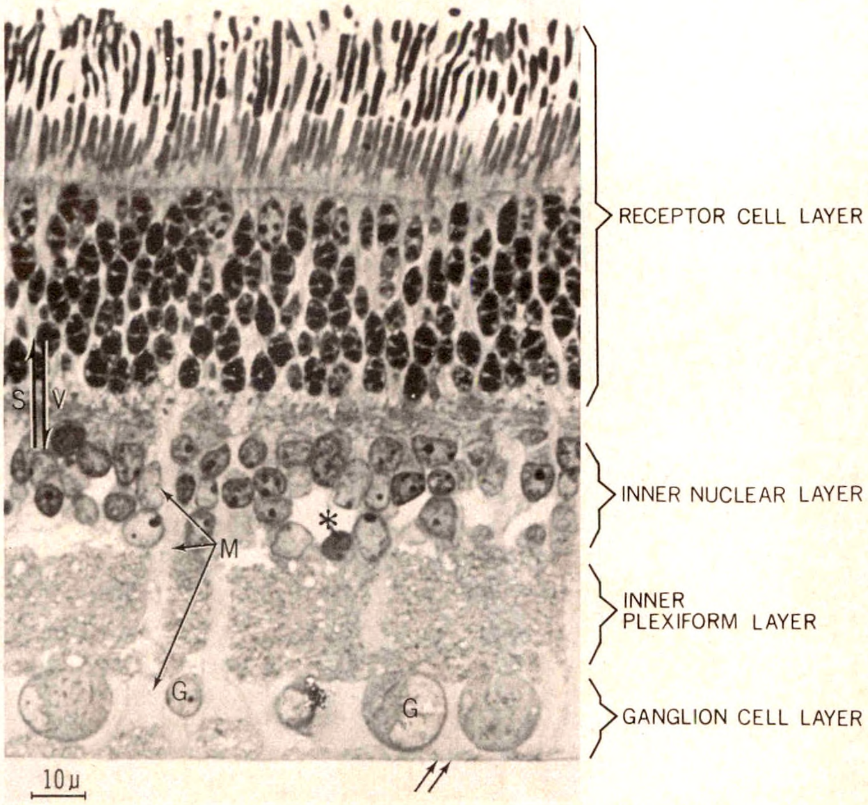

Fig 2.—Control retina incubated 120 minutes. Photomicrograph (dry objective, numerical aperture = 0.65) of 1μ section of Epon-embedded retina. Asterisk indicates unstained polygonal spaces in inner nuclear layer not representative of tissue damage (see "Results"). In control retinas, receptor cell nuclei were bilobed and there was little perinuclear space. Nuclei of all other cells showed relatively uniform karyoplasm, with exception of prominent nucleoli in cells of inner nuclear layer. Inner plexiform layer of controls (layer of synapses among neurons of inner nuclear layer and ganglion cells) was compact, containing only occasional, lucent circular profiles. Ganglion cells (G) were round, with cytoplasm typically staining more densely than nuclei or surrounding Mueller astroglial cell processes (M). Profile of the inner limiting membrane (vitread surface of retina [double arrow] was always smooth and devoid of blebs or other excrescences. For detailed description of Mueller's astroglial cell, see Fig 4. Opposed half arrows on the left side of figure indicate directions within retina toward sclera, or slerad (S), and toward vitreous, or vitread (V). Either of these directions are termed "radial" in the retina (toluidine blue, bar = 10μ).

clearly in Fig 4. Oxygen deprivation alone (Fig 3, bottom left) left cell structure of the inner nuclear layer and the ganglion cell layer relatively unaltered, even after 180 minutes. Receptor cells, however, were all killed by this deprivation. Glucose deprivation for 180 minutes (Fig 3, bottom right), on the other hand, presented an appearance similar to that of 90 minutes of open combined oxygen and glucose deprivation. That is, all the neurons of the retina were killed, but the Mueller cells retained normal structure.

Onset of Irreversible Pathological Changes

Deprivations sufficiently prolonged to reveal gross differences in vulnerability do not reveal the minimum lethal "dose" of deprivation for the more vulnerable cell types.

Closed system deprivation was in all respects the most harmful. It alone affected all cell types of the retina within the times studied. Closed deprivation initiated irreversible damage with the "smallest dose" (briefest time) of the four deprivations, although its greater severity for neurons compared with combined oxygen and glucose deprivation was slight and possibly not significant. Retinas were essentially normal on resupply after ten, 20, or 30 minutes of closed deprivation, although occasional pyknotic cells could be observed after 30 minutes' deprivation. However, after 40 minutes' closed deprivation followed by one hour resupply, all cells of the retina appeared severely damaged, with widespread hyperchromasia in the receptor cell layer, swollen cells and cells with nuclei with segregated chromatin predominated in the inner nuclear layer, and the inner plexiform layer was spongiform. Ganglion and Mueller cells presented structural abnormalities similar to those observed after 90 minutes' closed system deprivation.

Combined oxygen and glucose deprivation of 20, 30, and 40 minutes permitted recovery (or retention) of normal morphology and was thus similar to 30 minutes' closed deprivation. (Because of the presence of some cells with abnormal nuclei along the sclerad side of the inner nuclear layer, it is possible that horizontal cells may have been selectively affected by this deprivation.) After 60 minutes' combined oxygen and glucose deprivation, about two thirds of the receptor cells were either swollen or hyperchromic, and about two thirds of the specimens showed swollen neurons in the inner nuclear layer and spongiform change in the inner plexiform layer. Most ganglion cells were normal. As would be expected from the normal appearance of Mueller cells in retinas deprived for 90 minutes, Mueller cells appeared quite normal after 60 minutes of combined oxygen and glucose deprivation.

The appearance of retinas *deprived of oxygen alone* for 60 minutes in the presence of 10 mM glucose and then resupplied was essentially normal. However, by 80 minutes of oxygen deprivation alone, numerous hyperchromic cells were found in the receptor cell layer after resupply. The remaining layers of the retina were similar to controls.

Glucose deprivation for 140 minutes in the presence of oxygen did not result in irreversible changes in any

Table 1.—Experimental Material: Number of Retinas

Condition	Minutes of Incubation																				Total
	5	10	15	20	30	40	50	60	70	80	90	100	110	120	140	160	180	200	240	300	
Control*	2		2		1						2	9		4			1	1	1	1	**24**
Deprived† Closed system		1		2	1	2	1	3			1										**11**
Oxygen and glucose deprived				2	1	3		9	3		2										**20**
Oxygen deprived								1	1	1	2	2	1	2			1				**11**
Glucose deprived											2		1	1	1	1	1				**7**
Total																					**73**

*Refers to minutes in control medium.

†Refers to minutes in deprivation medium. All retinas were then resupplied with oxygen and glucose for at least one hour.

but a subpopulation (horizontal cells?) of the inner nuclear layer. By 160 minutes of glucose deprivation alone, the receptor cells were all swollen after resupply.

Table 2 summarizes these findings. Receptor cells (and possibly horizontal cells) were the most vulnerable to irreversible damage due to acute oxygen deprivation, glucose deprivation, or both combined. Mueller cells were as vulnerable or less so than the *least* vulnerable neurons.

Table 2.—Intervals of Deprivation Time Between Irreversible Structural Changes First Appearing and These Changes Becoming General*

Cell Type	Type of Deprivation, min			
	Closed System	Oxygen and Glucose	Oxygen	Glucose
Receptor cells	30-50	40-70	80-100	160-180
Neurons of inner nuclear layer†	40-50	40-70	>180	180-180
Ganglion cells	40-50	40-90	>180	180->200
Mueller cells (neuroglia)	40-50	>90	>180	>200

*"First appearance" was operationally defined as the earliest time at which more than roughly 10% of a given cell type was affected. Changes were considered to have become "general" when about 90% or more cells were irreversibly damaged.

†Cells along the sclerad border of the inner nuclear layer were affected somewhat earlier than the rest of the neurons in this layer.

COMMENT

The primary objective of this study was to establish time factors for irreversible structural damage of different cell types in the retina under different conditions of oxygen and/or glucose deprivation, ie, the "dose" of a given deprivation necessary to kill a given kind of cell. Changes evident in the light microscope must represent serious alterations of cell structure. We have taken *any* differences compared with controls that still remained after resupply of oxygen and glucose as evidence of irreversible damage. For the present purposes, the details of such structural damage are of less importance than its presence, and we have presented no data on changes occurring during deprivation.

Relation of Present Morphologic Findings to Findings by Other Methods

Previous studies of deprived isolated retina where opportunity for recovery was afforded have shown the following: Optic nerve compound action potential in response to light flashes recovered after 20 minutes of combined oxygen and glucose deprivation at 37 C but was irreversibly lost after 30 minutes.[8] Webster and Ames[2] reported irreversible mitochondrial swelling after 30 minutes' open combined oxygen and glucose deprivation. Protein sythesis of isolated rabbit retina (J. M. Parks, PhD, unpublished data) was irreversibly diminished to 10% of control synthesis after 60 minutes' closed system deprivation. At 90 minutes of combined oxygen and glucose deprivation, approximately 25% of control synthesis survived, probably reflecting continued survival of Mueller cells. Parks et al (see p 709) studied the reversibility of cell swelling after oxygen and glucose deprivation, using radioactive inulin as an extracellular marker. In retinas deprived 50 minutes or more, intracellular water accumulation could not be reversed by resupply of oxygen and glucose. In the same study, a pathological increase in cell permeability to mannitol was found after 50 minutes' oxygen and glucose deprivation, which was not reversed by resupply. Thus, the time factors for irreversible damage to retinal cells as assessed by structural changes in our study do not appear to be very different from previous determinations by other methods.

Relation of Experimental Conditions to Ischemia in Vivo

As with any proposed in vitro model of an in vivo process, it is necessary to establish grounds for acceptance of the appropriateness of the model conditions. We have subjected retinas to various conditions of deprivation of oxygen and glucose. It is generally believed, but as yet not empirically

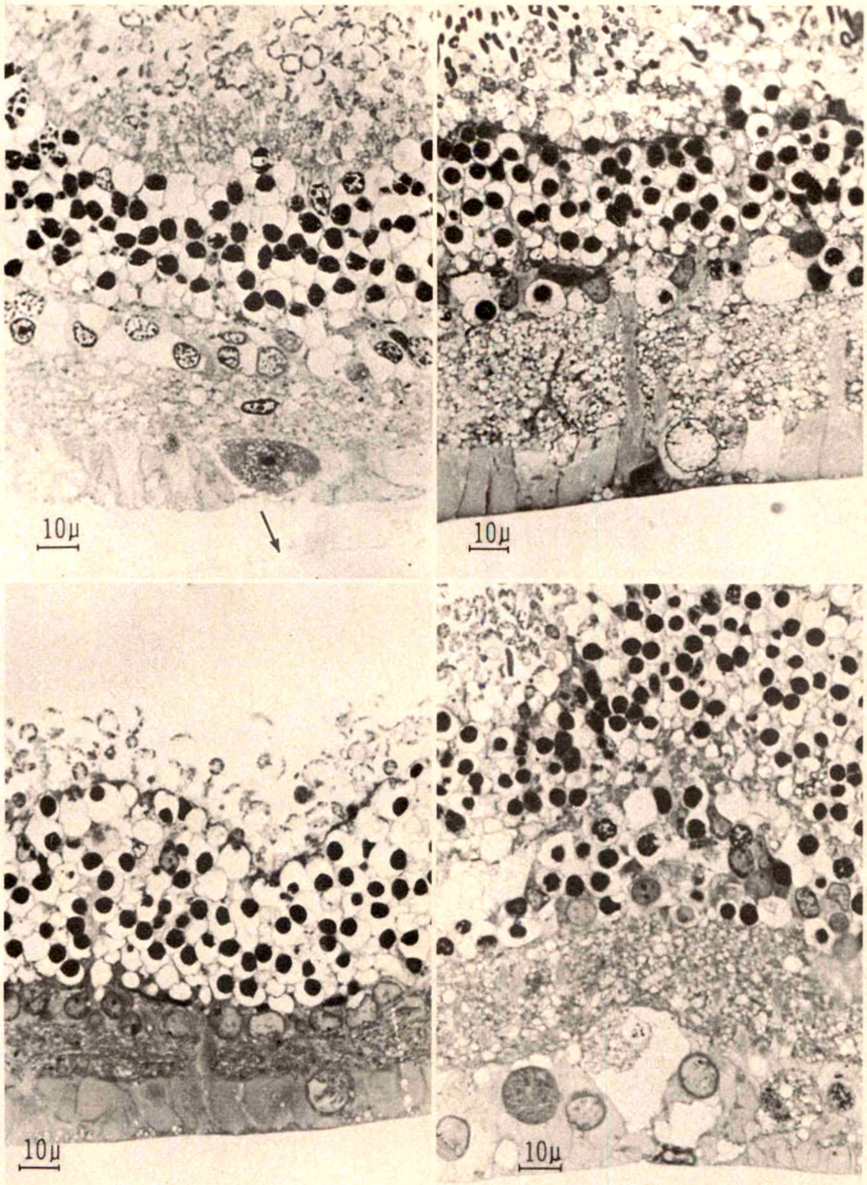

Fig 3.—Prolonged deprivation followed by resupply of oxygen and glucose (technical information as in Fig 2). Top left, Ninety-minute "closed system" deprivation followed by resupply. Receptor cells were grossly swollen with pyknotic, unlobed nuclei. Cells of inner nuclear layer were swollen with heterochromatic nuclei. Inner plexiform layer was finely vacuolated, giving this layer a spongiform appearance. Ganglion cells were either pyknotic or swollen. Arrow indicates delicate layer of Mueller cell blebs beyond inner limiting membrane. For further description of Mueller cell changes, see legend to Fig 4. Top right, Ninety-minute oxygen and glucose deprivation followed by resupply. Receptor cells, neurons of inner nuclear layer, and ganglion cells showed structural abnormalities similar to those after 90-minute "closed system" deprivation, except that nuclei of neurons of the inner nuclear layer were pyknotic rather than speckled. Mueller cells (astroglia) were normal. See Fig 4 for further detail. Bottom left, One hundred and eighty minute oxygen deprivation in presence of 10 mM glucose followed by resupply of oxygen. Receptor cells were grossly swollen and in other respects showed similar structural abnormalities to those in closed system deprivation and combined oxygen and glucose deprivation. Cells of inner nuclear layer, inner plexiform layer, and ganglion cell layer all appeared normal, except that polygonal lucent spaces in inner nuclear layer observed in controls after prolonged incubation were rarely encountered. Bottom right, One hundred eighty minute glucose deprivation in presence of 95% O_2 followed by resupply of glucose. Structural abnormalities in light microscope were similar in all respects to those observed after 90 minutes' combined O_2 and glucose deprivation, except that a substantial proportion of ganglion cells retained a normal appearance. As with combined O_2 and glucose deprivation, Mueller cells appeared normal.

well demonstrated, that deprivation of the substances required for metabolic energy production is the operative variable in ischemic cell death. We believe that these components of in vivo ischemia have been separately and appropriately reproduced in our conditions of incubation in the absence of oxygen or glucose or both. However, it is evident that in totally ischemic brain, cells have only a limited volume of interstitial fluid with which to exchange, and the tissue is converted to a "closed system." With cessation of blood flow, the composition of the interstitial fluid is no longer maintained constant. We believe that our "closed system" deprivation superimposes on the combination of oxygen and glucose deprivation the loss of homeostasis of the concentrations of other components of the interstitial fluid.

Relation of Findings to Retinal Ischemia in Vivo

Our experimental condition of oxygen and glucose deprivation has some features in common with in vivo retinal ischemia induced by elevation of intraocular pressure above systolic arterial pressure, but is probably a more severe deprivation. During ocular pressure ischemia, retinal cells have access to the vitreous humor as a small but possibly important reservoir of O_2 and glucose, and a large sink to "buffer" the composition of the interstitial fluid. Popp[9] found complete recovery of the electroretinogram after 30 minutes' ischemia and partial recovery thereafter until 105 minutes. Reinecke et al[10] found morphologic recovery after 60 minutes' ischemia, but retinal necrosis after 90 minutes. In the latter experiments, cessation of blood flow was verified by funduscopy.

Relation to Findings on Brain Slices

Studies of *reversibility* of tissue changes due to different deprivations using brain slices have been limited. Yamamoto and Kurokawa[11] found irreversible depression of electrical responses and adenosine triphosphate (ATP) after 30 minutes' *combined O_2 and glucose deprivation*, but not after

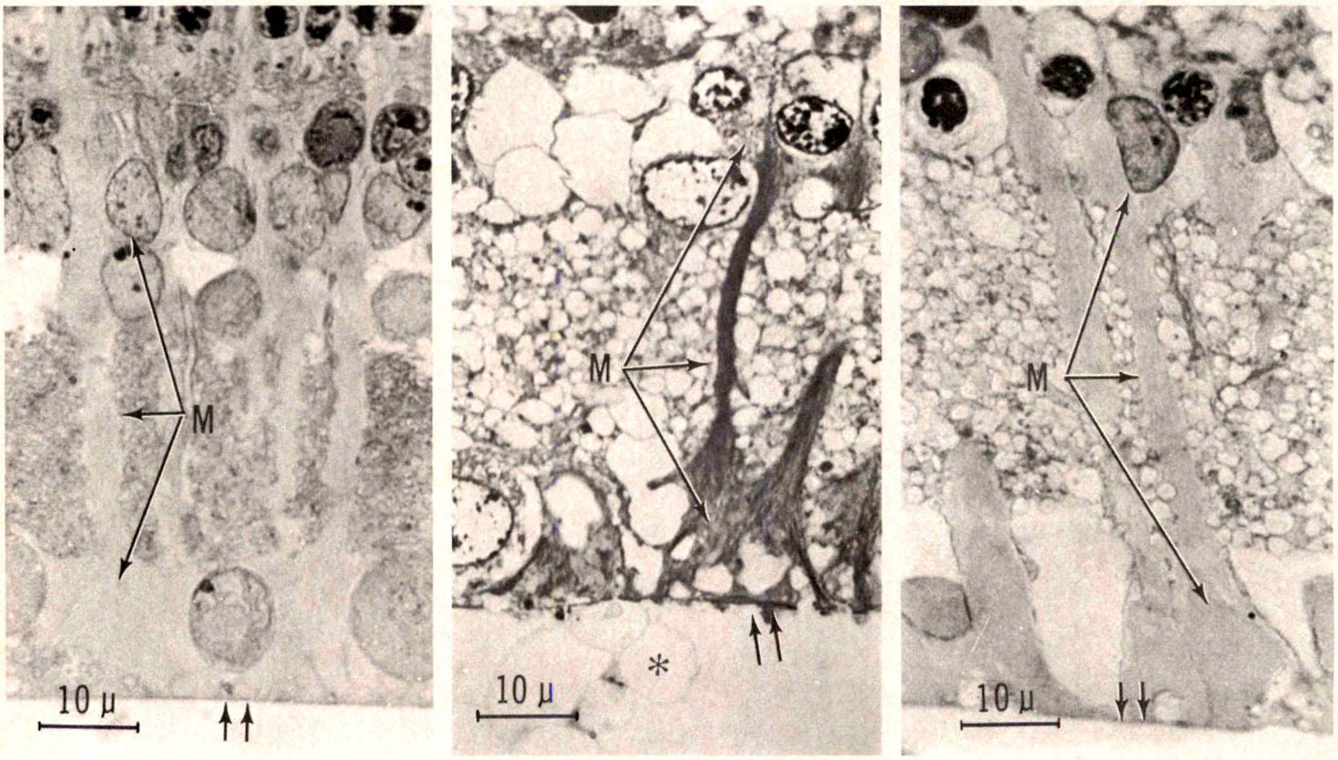

Fig 4.—Mueller astroglia—cell bodies in inner nuclear layer and processes in inner plexiform and ganglion cell layers. M indicates Mueller cell; double arrow, inner limiting membrane. Photomicrograph (oil immersion objective, numerical aperture = 1.32) embedding, sectioning, and stain as in Fig 2. Left, Control incubated 120 minutes. Mueller cell nuclei were generally reniform with fairly homogenous karyoplasm. Columnar Mueller cell processes penetrated radially through inner plexiform layer and expanded to form bulk of ganglion cell layer. Vitread surface of retina, inner limiting membrane (double arrows), was formed from mosaic of these expanded Mueller cell processes. Profile of inner limiting membrane was always smooth and without excrescences of any kind in controls. Center, Ninety-minute "closed system" deprivation followed by resupply. Mueller cell nuclei were heterochromatic and surrounded by granular, coagulated-appearing cytoplasm with moderate swelling of perikarya. Cytoplasm of Mueller cell processes in inner plexiform and ganglion cell layers was hyperchromic or granular. Asterisk indicates numerous blebs found beyond line of inner limiting membrane. Profile of inner limiting membrane was irregular with numerous gaps and excrescences. Right, Ninety-minute combined oxygen and glucose deprivation followed by resupply. Mueller cell morphologic findings were similar to that of controls. Blebs and raggedness of inner limiting membrane were not observed under this condition.

15 minutes' deprivation. Yamamoto and co-workers[12] described irreversible change in fine structure under similar conditions. Swanson[13] reported substantial recovery of intracellular ions, creatine phosphate, and ATP in unstimulated slices after 45 minutes', but not after 60 minutes' *anoxia* alone in the presence of 10 mM glucose. Yamamoto and Kurokawa[11] reported nearly complete functional recovery, "even if *anoxia* lasted more than 30 minutes."

Vulnerability of Different Retinal Cell Types to Different Components of the Ischemic Condition

Mueller cells retained normal structure after combined oxygen and glucose deprivation more than twice as long as other cells. The resistance of Mueller cells was thus surprising, since astroglial swelling has been an early finding in ischemia in vivo.[14] We are not aware of other information concerning the survival of astroglia under conditions of oxygen and glucose deprivation in vitro. We have found the Mueller cells to be very vulnerable to closed system conditions. Elimination of the homeostatic effect of the large volume of incubating medium *reduced* permissible deprivation from more than 90 minutes of oxygen and glucose deprivation to about 40 minutes of closed system deprivation. We did not observe a similar effect with neurons, which suggests that a loss of homeostasis of the composition of the extracellular fluid is particularly damaging to astroglial cells. We conclude that Mueller cells are affected by some change in the composition of the extracellular fluid *other than* disappearance of oxygen and glucose.

It is not surprising that the receptor cells showed a selective vulnerability to oxygen removal in view of the high rate of ion pumping that these cells must sustain.[15] The apparent indifference (in the presence of 10 mM glucose) of the remaining cell layers to in vitro oxygen deprivation for at least 180 minutes may reflect peculiarities of the retina. However, it is also possible that brain neurons are not as dependent on oxygen for *survival,* as distinct from function, as is generally assumed. To our knowledge, experiments in which normal brain has been adequately perfused with oxygen-free but otherwise normal blood have not been performed. Any animal study that merely arrests respiration or gives oxygen-free breathing mixtures very rapidly becomes contaminated with failure of the circulation, and thus only for the first few minutes represents pure anoxia.[1]

Combined oxygen and glucose deprivation was more severe than either oxygen deprivation alone or glucose deprivation alone. The apparent greater severity of the closed deprivation for neurons should be viewed tentatively, because it is possible that studies on larger numbers of retinas would indicate similar times of onset of irreversible damage under both closed and open combined oxygen and glucose deprivation.

In view of the apparent dependence of receptor cells on glycolytic metabolism, as evidenced by their vulnerability to iodoacetate,[16] it is surprising that greater differences in vulnerability to glucose deprivation alone were not discerned between the receptor cells and the other neurons of the retina (Table 2). A substrate on which all of the retinal neurons could draw in common may be stored in the Mueller cells, which are known to contain a great deal of glycogen as well as the enzyme glucose-6-phosphatase.[17] This enzyme would make it possible for intracellular glucose originating from glycogen to be liberated into the extracellular space for use by other cells. Receptor cells, which seem most vulnerable to glucose deprivation, are exposed to the least volume of neighboring Mueller cell cytoplasm. Ganglion cells, which appear least vulnerable of the retinal neurons to glucose lack, are entirely surrounded by a thick layer of Mueller cell processes. Neurons of the inner nuclear layer appear to have intermediate vulnerability.

In this study, neurons and glia responded differently to the same insult and individual cell types had different responses to different insults. The extent to which these observations can be applied to brain cells remains to be clarified. However, retina is properly considered part of the CNS, albeit rather specialized. It derives embryologically from the forebrain,[18] lies "behind" the blood brain barrier,[19] and lays down central-type rather than peripheral-type myelin.[20] Despite some differences from the typical brain astrocyte, the Mueller cell is clearly an astroglial cell. Its content of fiber bundles and glycogen,[21] its ensheathing of the neurons, and the disposition of its processes on surfaces of the retina are all typical of astroglia in the brain proper.[18,22]

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Case Reports

Progressive Rubella Panencephalitis

Jerry S. Wolinsky, MD; Bruce O. Berg, MD; Charles J. Maitland, MD

• A patient with progressive rubella panencephalitis developed initial symptoms of neurologic deterioration 12 years after childhood German measles. Progressive rubella panencephalitis should be considered in adolescents with progressive dementia attended by pyramidal and cerebellar dysfunction.

(*Arch Neurol* 33:722-723, 1976)

The dramatic effects of rubella infection on the developing nervous system have been well recognized.[1,2] While the consequences of in utero rubella infection on neural tissue may be severe, the clinical defects produced have been thought to be static.[3,4] Recently, however, a syndrome of delayed progressive neurologic deterioration has been described in children with the stigmata of congenital rubella.[5-7] Recovery of rubella virus from the brain of one affected child suggests a latent or persistent role for the virus.[6,8] One patient with a similar illness demonstrated none of the stigmata of congenital rubella; the acquisition of rubella was not recorded but assumed to be postnatal.[9] We report on one patient with progressive rubella panencephalitis (PRP) who had a history of earlier childhood rubella infection.

REPORT OF A CASE

The patient, a 19-year-old man, was referred for evaluation of dementia. He was a product of a full-term, normal gestation, labor, and delivery; the developmental milestones were normal. In 1960, at age 7, malaise and a generalized rash developed, and a diagnosis of German measles was made. His mental and motor development were normal. He completed high school at age 18 with a B+ average. One year later, while in commercial college, he was noted to be clumsy and to fall frequently. He later became dysarthric, and because his family doctor thought that he was somewhat demented, he was referred for neurologic examination.

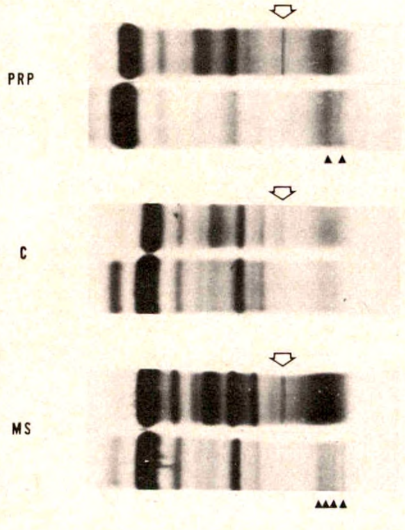
On examination he was a well-developed 19-year-old with none of the stigmata of congenital rubella; he seemed somewhat demented and dysarthric. Cranial nerves were normal except for end-point nystagmus in all directions of gaze. The gait was unsteady, broad-based, and somewhat stiff. He had marked truncal and limb ataxia, and titubation was apparent. There was no loss of muscle bulk or strength; tone was moderately increased throughout. The deep tendon reflexes were symmetrically hyperactive and the plantar responses were extensor.

Results of routine blood and urine studies were normal. The cerebrospinal fluid (CSF) was clear, without blood cells; the glucose level was 55 mg/100 ml; and the protein level was 104 mg/100 ml, with a 38% γ-globulin concentration on protein electrophoresis. An electroencephalogram was abnormal with moderate widespread low to medium beta activity, and occasional bursts of rhythmic delta activity, 2 to 3 Hz, in frontal leads. A pneumoencephalogram showed moderate generalized ventricular enlargement. The cisterna magna was very large and there was minimal dilation of cerebral sulci. Cerebrospinal fluid and blood serology were negative for rubeola, herpes simplex, and mumps virus.

Psychometric assessment on the Wechsler Adult Intelligence Scale (WAIS) showed a full-scale IQ of 65, with a verbal IQ of 71 and performance IQ of 62. There was moderately severe constructional dyspraxia, spelling dyspraxia, and dyscalculia with mild right-left disorientation. The patient had little immediate recall of verbal, numerical, and configurational material. He was discharged with a diagnosis of leukoencephalopathy of undetermined origin.

The patient's condition was reevaluated two years later because of progressive neurologic deterioration. Speech was slow and dysarthric. The optic disks were pale with widespread loss of retinal nerve fibers. Extraocular motility was full, with saccadic movements. A mild right central facial paresis and hyperactive jaw jerks were present. There was generalized, moderately severe increase in muscle tone with symmetrically hyperactive deep tendon reflexes, sustained ankle and knee clonus, and extensor plantar responses. Bilateral hand and foot grasps were evident. The patient had truncal and limb ataxia with titubation and his gait was wide-based and ataxic; he was unable to stand unassisted. No sensory abnormalities were noted. Psychometric testing showed a WAIS full-scale IQ of 51; verbal IQ of 58; and performance IQ of 48.

Agarose gel electrophoresis of undiluted serum (above) and concentrated cerebrospinal fluid (below) from patient, compared with control (C) and multiple sclerosis (MS) sample. Open arrows indicate site of sample application. Two distinct bands (solid triangles) noted in γ-globulin region of PRP patient and multiple bands in MS sample contrast with diffuse pattern seen in control.



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Serologic Studies

Date of Sample	Source	Titer by Hemaglutination Inhibition*						
		Rubella (CF)†	Rubella	Measles	PI (1-4)†	Mumps	HSV†	CMV†
2/23/73	Serum	128	128	< 8	< 8	< 8	< 8	< 8
1/21/75	Serum	128	128	< 8	< 8	< 8	< 8	< 8
	Cerebrospinal fluid	8	16	< 8	< 8	< 8	< 8	< 8

*Expressed as reciprocal of dilution of serum or cerebrospinal fluid.
†CF indicates complement-fixation; PI, parainfluenza virus; HSV, herpes simplex virus; and CMV, cytomegalovirus.

The EEG was abnormal, with diffuse theta activity and the occasional appearance of periodic high-amplitude slow transients at 1.5 to 2 Hz in the frontal leads. These complexes occurred once every five to eight seconds, lasting one second at amplitudes sometimes exceeding 500 μv. These complexes were not apparent on subsequent tracings. Computerized axial tomographic (CT) scans demonstrated moderate symmetrical ventricular enlargement.

The CSF contained three lymphocytes per cubic millimeter and the protein level was 96 mg/100 ml, with 36% γ-globulin concentration. Serum and CSF rubella complement-fixation and hemagglutination inhibition antibodies were elevated, with an elevated CSF-serum ratio (Table). Agarose gel electrophoresis of the CSF showed an oligoclonal pattern (Figure). The patient's condition has continued to deteriorate.

COMMENT

The recently recognized syndrome of progressive rubella panencephalitis appears with insidious deterioration of motor and mental function during the second decade of life. Pancerebellar dysfunction with marked ataxia has been a dominant feature. Conventional neurodiagnostic tests are nonspecific in this syndrome, although the pneumoencephalogram has consistently revealed panventricular enlargement and a capacious cisterna magna. The CSF protein electrophoresis characteristically shows marked elevation of γ-globulin levels. Oligoclonal bands have been noted in the γ-globulin region with agarose gel electrophoresis in one previous patient.[10] The elevated CSF-serum ratio of rubella specific antibody has been found in all previously tested patients. A subacute or chronic panencephalitis has been demonstrated in brain biopsy material[5,6] or autopsy material[5,7] from three of the patients. The recovery of rubella virus from brain biopsy material from one patient[6,8] suggests a role for persistent rubella virus in the pathogenesis of this syndrome.

In the present patient, the clinical presentation was consistent with a progressive panencephalitis with prominent cerebellar involvement. Panventricular enlargement and a prominent cisterna magna were evident by pneumoencephalogram and CT scan, and the CSF showed greatly increased levels of gamma globulin with an oligoclonal pattern on agarose gel electrophoresis. Serologically, there was evidence of infection at some time with rubella virus, and the CSF-serum rubella antibody ratio was elevated. These findings are all consistent with a clinical diagnosis of PRP in this man.

Four of the five previously reported patients with PRP have shown stigmata of congenital rubella. Children exposed in utero to rubella may have elevated antibody titers to the virus without clinical disease[11]; therefore, in patients with PRP who lack stigmata of congenital rubella, the absence of a history of childhood German measles makes it difficult to ascertain whether the virus was initially acquired in utero or postnatally. Our patient had none of the stigmata of congenital rubella and a history of a clinically diagnosed rubella infection at age 7. Further, there was no serologic evidence for prior infection with rubeola. Thus, in this case it appears likely that the initial rubella virus infection was acquired in early childhood.

Progressive rubella panencephalitis should be considered in the differential diagnosis of progressive neurologic deterioration occurring in late childhood or early adolescence whether or not there is a history of maternal rubella or stigmata of congenital rubella. Clinical suspicion of the syndrome should be high in cases of progressive mental and motor deterioration accompanied by prominent cerebellar dysfunction. Serologic studies for rubella virus and cerebrospinal fluid-serum antibody ratios should be determined in patients with otherwise unexplained elevations of cerebrospinal fluid γ-globulin levels.

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Familial Fingerprint Body Myopathy

Michel Fardeau, MD; Fernando M. S. Tomé, MD, PhD; Serge Derambure, MD

• Muscle biopsy specimens from two half brothers with a congenital benign muscle disorder and from their mother, clinically unaffected, were studied by histochemistry and electron microscopy. In the children's biopsy specimens, the ultrastructural examination showed numerous fingerprint bodies located at the periphery of the muscle fibers. The histochemical pattern was different in these two specimens. In the mother's biopsy specimen, while fingerprint bodies were not found, the muscle fibers showed slight but definite changes. Even if the fingerprint bodies by themselves are not specific for a particular muscle disease, their occurrence in two half brothers is a valid argument in favor of the individualization of the fingerprint body myopathy, which has been previously described.

(*Arch Neurol* 33:724-725, 1976)

In 1972, Engel et al[1] described a new type of congenital muscle disease characterized by the presence of numerous inclusions with a fingerprint appearance within the muscle fibers. Since then, similar inclusions have been reported in many different muscle disorders.[2-4] Consequently, their specificity for a particular muscle disease has been questioned.

The demonstration of fingerprint bodies in the muscle biopsy specimens of two half brothers with a slowly progressive congenital muscle disorder discussed here gives strong support to the individualization of the fingerprint body myopathy.[1]

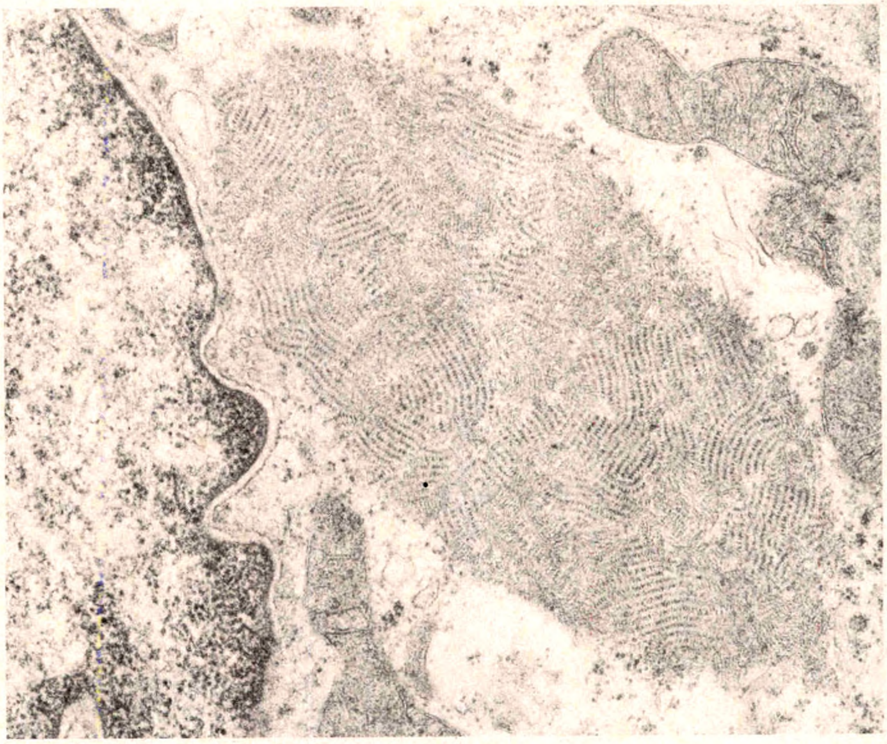
REPORT OF CASES

CASE 1.—A 13-month-old boy was born cyanotic and had generalized hypotonia since birth, predominating in the trunk and upper limb muscles; the proximal muscles were moderately atrophic. He sat without support at 1 year and had a notably kyphotic posture. Deep reflexes were normal. Mental development appeared normal. The electromyogram, creatine phosphokinase level, and karyotype were normal.

CASE 2.—A 12-year-old boy, half brother of the previous patient, had considerable motor disturbances since birth, walked at 3 years of age, and had diffuse muscle atrophy predominating in the distal segments of the limbs. He had kyphosis and pectus excavatus. Deep reflexes were normal. He seemed of subnormal intelligence. Creatine phosphokinase level was elevated (146 IU).

CASE 3.—The children's mother, 32 years old, never complained of any muscle defi-

One of numerous fingerprint bodies seen in biopsy specimen of patient 2. It lies in peripheral part of muscle fiber, close to nuclear pole (original magnification ×25,500).



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ciency. Findings from a neurological examination were normal. She had another child, an older sister of patient 1, who was considered normal. She belonged to a large kindred: two brothers and five sisters. Two of her sisters had children with hip dislocations.

METHODS

Muscle biopsies were performed in the deltoid (case 1), peroneus brevis (case 2), and biceps (case 3). The specimens were studied by light microscopy in frozen sections and by light and electron microscopy in araldite-embedded sections. The techniques used were described in previous reports.[5]

RESULTS

In case 1, the muscle fibers exhibited a slight variation in diameter. The relative proportion of the different histochemical fiber types was normal (47% of type I; 53% of type II) and were distributed in a normal mosaic pattern. The mean diameter of type I fibers (13μ) was lower than that of type II (19μ). The majority of type II fibers was of type IIA. No structural changes were seen.

By electron microscopy, most fibers had a normal myofibrillar organization, but they contained numerous inclusions with a fingerprint appearance. These bodies were generally rounded or oval, located often in the neighborhood of a nucleus. They were formed by convoluted lamellae, lying 300 to 320 Angstroms apart in sections orthogonal to their planes. Each lamella had sawtooth-like densities, disposed in parallel, with a periodicity of 160 A; these densities were about 60 A wide and 160 A high.

Other changes were observed rarely: small foci of sarcomeric disorganization, streaming of the Z lines, stacks of rods, and concentric laminated bodies. Active satellite cells were frequent.

In case 2, the biopsy specimen showed only slight abnormalities by light microscopy: variation in diameter and segmentation of occasional muscle fibers. The histochemical techniques showed a predominance of type I fibers (ratio of type I to type II, 8:1). The type I fibers were smaller (46μ) than the type II (55μ); there was considerable variation in the diameter of type I fibers and, to a lesser extent, of the type II.

The ultrastructural findings were similar to those of the patient's brother. The muscle fibers rarely exhibited an abnormal myofibrillar arrangement, but often contained fingerprint bodies at their periphery (Figure).

In case 3, the muscle fibers showed a moderate variation in diameter, and some had central nuclei. The different histochemical fiber types had a normal pattern. Sections for oxidative enzymes demonstrated, in some fibers, a lobulated arrangement of the inner structure.

By electron microscopy, many fibers exhibited changes of the myofibrillar organization. In addition, a collection of finely granular material, not membrane-bound, was found near a nucleus, which could not be related to any normal component of the fiber. It reminded one of similar material sometimes seen in contiguity with the fingerprint inclusions in the other two cases. Typical fingerprint bodies were not found.

COMMENT

Fingerprint bodies have been observed in various conditions: congenital myopathy[1,6]; dermatomyositis (S. Carpenter and G. Karpati, oral communication, 1972); dystrophia myotonica[2,3]; oculopharyngeal muscular dystrophy[4]; and other disorders.[3] This enumeration clearly demonstrates the nonspecificity of these bodies. Nevertheless, their abundance and predominance over the other changes in two biopsy specimens of a 5-year-old girl, with a nonprogressive weakness and hypotonia since infancy, led Engel and co-workers[1] to regard the fingerprint bodies as "the distinguishing morphological feature" of a new type of congenital myopathy. Also under the headline of fingerprint body myopathy, Gordon et al[6] reported the case of a woman, aged 55, who had a chronic congenital myopathy and whose muscle biopsy specimen showed the presence of fingerprint bodies. The family described herein demonstrates for the first time to our knowledge, the familial incidence of the morphological abnormality and strongly supports the individualization of the entity, even if the morphological features are not specific.

Since the affected children are half brothers, their mother should be the transmitter of the condition. It was not possible to find typical fingerprint bodies in her biopsy specimen, but slight but evident changes occurred in the muscle fibers.

The histochemical pattern was different in the two children's biopsy specimens. In both, the type I fibers were smaller than the type II. However, there was a larger variation of the fiber diameters in case 2, and a notable type I fiber predominance occurred only in this case. Type I fiber predominance was also seen in the two previously reported cases,[1,6] one showing a relative type I smallness[1] and the other a large range of diameters for both types of fibers.[6] All these histochemical data cannot be compared strictly, because the muscles biopsied and the ages of the patients were different. However, these four observations demonstrate that the fingerprint body myopathy share different histochemical patterns that may be related to the stage of the evolution of the condition.

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Brain Stem Auditory-Evoked Responses in Suspected Central Pontine Myelinolysis

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• Central pontine myelinolysis was suspected in two chronic alcoholics who developed and recovered from a progressive spastic paresis of all muscles, that derived innervation at and below the level of the pons. In both cases, short-latency auditory-evoked responses aided in the diagnosis by indicating a slowing of conduction in the pontine auditory pathway, which varied in degree with the severity of the clinical manifestations of pontine demyelination.

(*Arch Neurol* 33:726-728, 1976)

The first seven waves in scalp recordings of the human auditory-evoked response occur within ten msec after stimulus and have amplitudes of less than a microvolt.[1] These seven vertex-positive potentials are believed to be the far-field reflection of sequential electrical events at successively higher levels of the brain stem auditory pathway.[2] Clinical and experimental evidence indicates that wave I originates in the acoustic nerve[3-6] and that wave V is generated in the midbrain, in and around the inferior colliculi.[5-8] The latency difference between waves I and V should therefore be inversely related to conduction velocity in the intervening pontine segment of the auditory pathway.

We recently made serial measurements of the differential latency of waves I and V in two patients believed to have central pontine myelinolysis (CPM) on clinical grounds. These evoked potential findings supported the clinical diagnosis of CPM in both cases.

METHODS

Brain stem auditory responses were evoked with 0.1-msec clicks presented monaurally through headphones at a rate of ten per second. Click intensity was 60 dB above the mean hearing threshold for normals (60 dB sensation level [60 dB SL]), but was altered when necessary to aid in the identification of response components. Brain electrical activity recorded from a pair of electroencephalographic disk electrodes at the vertex (C_z) and the mastoid ipsilateral to stimulation was differentially amplified 500,000 times and filtered through a bandpass of 100 to 3,000 hertz (3 dB down points). This activity was monitored continuously on an oscilloscope and averaging was not performed when it was contaminated with electromyographic activity or other artifact. The amplified and filtered signals recorded in the first 16 msec following each click were averaged with computers having either 31μsec or 78μsec sampling intervals (apertures). The average of 2,000 to 4,000 such responses was replicated at least three times on an X-Y plotter. The latency difference of waves I and V (I-V latency) could be measured to the nearest 0.1 msec and did not vary by more than 0.2 msec between runs; its upper limit of normal is 4.4 msec.

REPORT OF CASES

Case 1.—A cachectic 51-year-old man was admitted to the hospital on June 23, 1975. He had a 33-year history of heavy alcohol abuse and a recent history of vomiting and diarrhea. Ten days prior to admission, he had difficulty standing and walking, and two days prior to admission, he had been unable to get out of bed. Mental status and cranial nerve function were normal, but there was prominent weakness of all proximal muscles. Muscle stretch reflexes were normal except for absent ankle jerks; plantar responses were flexor. Pain, touch, and vibratory sensations were moderately decreased in feet and ankles but were normal at the knees and elsewhere. Laboratory evaluation showed mild hypokalemia, hypomagnesemia, hypoproteinemia, and elevated serum glutamic oxaloacetic transaminase level, but results of all other studies (including serum B_{12} level) were normal.

After three weeks of fluid, electrolyte, and high-dose B-vitamin therapy, and following resolution of pneumococcal pneumonia, the patient's neurologic condition rapidly deteriorated. On July 16, 1975, he had severe weakness of all facial, glossopharyngeal, and extremity muscles, and was unable to lift his head, arms, or legs. Muscle stretch reflexes were all markedly hyperactive, including the jaw jerk, and the plantar responses were extensor. Mental status remained unchanged and brain scan, EEG, lumbar puncture, and nerve conduction velocities were all normal. Electromyography revealed minimal denervation in distal extremity muscles.

The I-V latency of the brain stem auditory-evoked responses was 4.2 msec at this time (within normal limits), and during the following week it remained at 4.3 ± 0.15 (SD) msec, as shown in the bottom left-hand portion of Fig 1, which plots the subsequent variation in the I-V latency during the entire hospital course. By July 29, 1975, the patient was completely paralyzed except for his extraocular muscles, and the I-V latency of the auditory-evoked response had increased to 5.1 msec. The visual-evoked response remained normal. For the following week, the patient was "locked-in"[9] and the I-V latency reached a maximum of 7.0 msec; during this period, the patient communicated appropriately with vertical eye movements and indicated that he had developed diplopia, had lost proprioceptive and vibratory sense in all extremities, and could no longer sense facial pinprick.

Slight voluntary movements of the distal extremities reappeared on Aug 6, 1975, and during the next seven weeks, a gradual but incomplete return of function to all paralyzed muscle groups occurred, paralleled by a progressive 0.4 msec per week decrease in I-V latency. On Sept 26, 1975, (week 11 of Fig 1), facial and glossopharyngeal weakness was minimal, the quadriparesis was slowly resolving, and the I-V latency had returned to normal. One month later, the brain stem auditory response was essentially unchanged, with a I-V latency of 4.3 msec; the patient then had only mild upper extremity weakness and moderate lower

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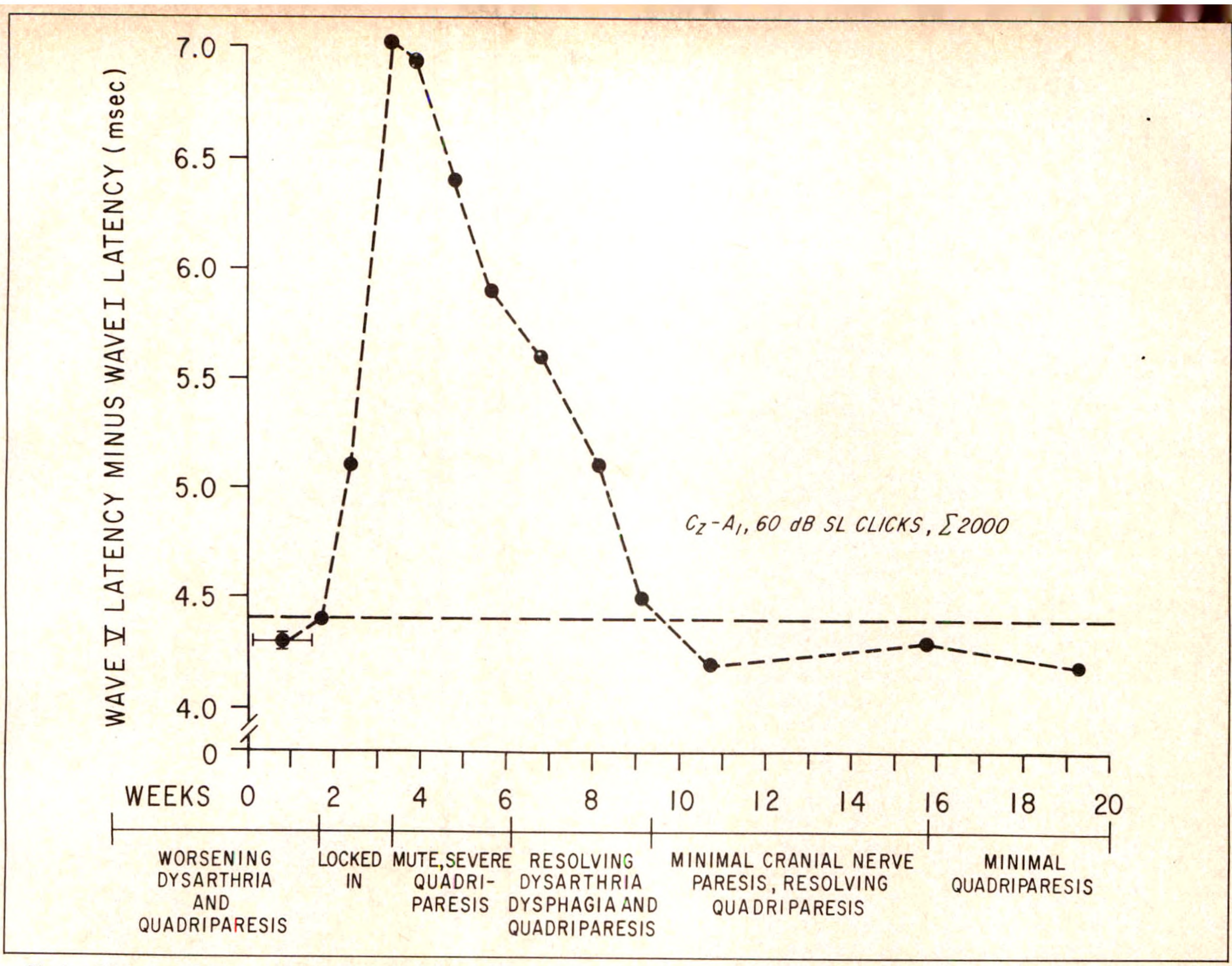

Fig 1.—Clinical correlates of I-V latency changes in case 1 during 20-week period from July 13 to Nov 30, 1975. Values from eight separate recording sessions in first ten days of testing (horizontal bracket) are pooled in first value, which has standard deviation indicated by vertical bracket. Horizontal dashed line indicates upper limit of normal for I-V latency. C_z-A_1 indicates vertex to left mastoid bipolar recording; dB SL, dB sensation level.

extremity weakness. Nearly identical responses were recorded three weeks later (week 20 of Fig 1), at which time he could walk without assistance.

Case 2.—A 48-year-old man with a 30-year history of chronic alcoholism was admitted on Sept 2, 1975, after two weeks of epigastric pain, nausea, and vomiting. He was jaundiced and cachectic and had hepatomegaly, mild generalized hyperreflexia, bilateral extensor plantar responses, and decreased vibratory and position sense of the feet. Results of liver function tests were abnormal and a liver biopsy confirmed the diagnosis of alcoholic hepatitis. After the first nine days in the hospital, during which the patient received multivitamin therapy (including 700 mg of thiamine by mouth, daily), the hepatitis began to resolve. However, on Sept 11, 1975, he developed diplopia and horizontal nystagmus, and during the following four days, he became dysarthric, dysphagic, quadriparetic, and developed ankle clonus and greater hyperreflexia. The jaw jerk became hyperactive, corneal reflexes diminished, facial pinprick sensibility decreased, lateral-gaze paresis worsened, and he was unable to arise from bed without assistance. Brain scan, EEG, serum B_{12} level, lumbar puncture, EMG, and nerve conduction velocities were normal.

The brain stem auditory responses shown in Fig 2(A) were recorded on Sept 15, 1975, when the signs of corticobulbar and corticospinal tract involvement were most severe. The component tentatively identified as wave V had its peak latency 8.4 msec after wave I. During the following 11 days, the dysarthria, dysphagia, facial, and extremity weakness gradually improved, and on Sept 26, 1975, the I-V latency had decreased to 5.9 msec and wave V had increased in amplitude relative to earlier waves (Fig 2, B). By Oct 31, 1975 (Fig 2, C), the I-V latency further decreased to 4.6 msec as the facial and glossopharyngeal weakness resolved and extremity strength improved, leaving only minimal to moderate weakness of limb muscles. Residual diplopia, horizontal nystagmus, mild generalized hyperreflexia, and decreased left facial sensation to pinprick had all improved by Dec 31, 1975, when the I-V latency was again normal (Fig 2, D).

COMMENT

As in two previous reports of clinically diagnosed CPM, the diagnosis in the cases above was based on (1) the history of chronic alcoholism with a superimposed illness; (2) signs of slowly progressive suprasegmental motor system disease, which resulted in paresis of all muscles deriving innervation at and below the level of the pons; and (3) preservation of consciousness and higher cerebral functions.[10,11] The development of the neurologic syndrome in the face of

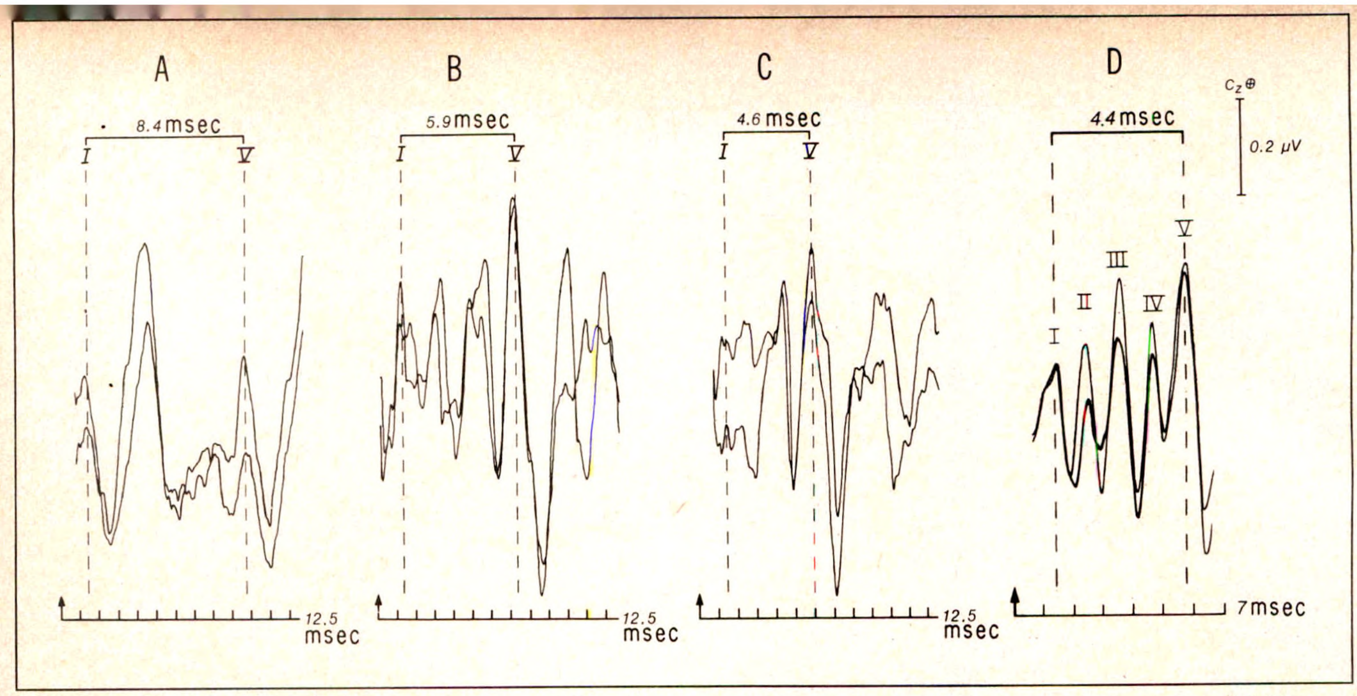

Fig 2.—Progressive decrease in I-V latency paralleling neurologic recovery in case 2. All tracings are the average of 2,000 responses to a 60 dB sensation level click delivered to left ear at the arrows and recorded from C_z-A_1. Initial 0.5 msec containing stimulus artifact has been deleted from three of the tracings. Note different time base for recording D, which was the first tracing in which wave IV could be clearly identified. Wave IV is fused with V in recordings B and C. A, Recordings from Sept 15, 1975; B, recordings from Sept 26, 1975; C, recordings from Oct 30, 1975; D, recordings from Dec 31, 1975.

general medical improvement is another common feature of this disease.[11]

The lesion of CPM begins in the median raphe of the basis pontis, spreads centrifugally in a diamond or "T" shape, and is characterized histologically by loss of myelin sheaths and oligodendroglia but relative sparing of axis cylinders and neurons.[12] Although this lesion would seem to be reversible to some extent, recovery from clinically suspected CPM has not previously been reported. The demyelination of CPM may extend dorsally into the ventral portion of the pontine tegmentum, as in three of the first four reported cases, in which there was demyelination of the medial lemnisci.[12] In two of those cases, in which the tegmentum adjoining the basis pontis was "unusually soft and gray," there had been somatosensory as well as motor deficits clinically; in one patient who had developed decreased corneal reflexes, the entering trigeminal root fibers were involved by the lesion. Sensory deficits that were compatible with trigeminal and medial lemniscal involvement were also observed in our patients.

Auditory tracts and nuclei of the caudal and mid-pons are situated ventrally in the tegmentum, adjacent to the basis pontis. Involvement of the auditory pathway at this level by CPM, either directly by demyelination or indirectly by edema, may account for the reversible prolongation of the I-V latency in the patients described here. Although we lack pathologic verification of the diagnosis in our patients, the clinical evidence of CPM is strong, and the electrophysiologic evidence for slowed conduction velocity in the ascending pontine auditory pathway closely paralleled the clinical manifestations of disease in adjacent descending motor tracts. If the diagnosis of CPM is correct, the fact that these patients presented within a short interval at the same medical center and the fact that they both recovered imply a greater incidence and better prognosis than has generally been assumed. It is probable that brain stem auditory responses can aid in the diagnosis of CPM and provide prognostic information about the progress of pontine demyelination or remyelination.

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Reginald Bickford, MB, FRCP, supplied the recording and computing equipment.

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Letters and Clinical Notes

Visuospatial Disorientation by a Mesencephalic Lesion in Man

To the Editor.—We were particularly interested in Denny-Brown's and Fischer's article[1] about the subcortical visual direction of behavior in monkeys, because their study helped explain a puzzling defect of spatial orientation in Parinaud syndrome. These cases are rare ("... of special interest that humans ... have not also presented spatial disorientation ....").

A 42-year-old man, previously in excellent health, suddenly experienced diplopia in all directions of gaze. When he tried to walk he was unsteady and veered to the left, without vertigo. A few hours later that day he was alert and gave a clear history. There was no nuchal rigidity. Gait and Romberg sign showed consistent deviation to the left. The right pupil was slightly smaller than the left, but there were normal responses to light. Bilateral retraction of the eyelids was also present. The left eye was depressed below the horizontal in primary position, increasing on looking to the left, while the diplopia could not be attributed to a particular eye muscle (skew deviation). There was similar mild depression of the right eye on right lateral gaze. Horizontal eye movements were not impaired in range, and there were normal horizontal optokinetic responses. Paralysis of upward gaze (on command, pursuit, and oculocephalic) and of convergence was present, but there was no retractory-convergence nystagmus and no head tilt. There was left (central) facial hypotonia, with slight weakness, and it was sometimes noted that the left arm dangled uselessly. On testing of separate muscles there was no weakness in this arm, but it was hypotonic, and drifted downwards when held outstretched with eyes closed.

Pseudo-athetoid movements of the fingers of the left hand were seen. When the patient was asked to bring both hands together, he reached with his right arm to the left, found the left hand after some groping around, and brought it to the midline. We expected to find profound disturbances of position sense in the left arm, but this proved to be normal. Perception of pinprick and cotton wool, vibration sense, graphesthesia, two-point discrimination, and stereognosis were also intact. There was equivocal visual inattention, no sensory inattention, no finger agnosia, and the patient could quickly grasp his right ear with his left hand. Some hypotonia of the left leg was found, but otherwise the lower limbs were normal. The patient denied any distortion or unfamiliarity in the perception of his body and surroundings.

During this first day he was drowsy, but th following morning he was alert, with no amnesi By then all abnormalities of the left arm ha disappeared, the gait had become normal, and only a trace of the left facial weakness remained. The cerebrospinal fluid was normal. One week after the onset the patient faultlessly compared the slope of given lines in both visual fields with those of a standard.[2] The oculomotor signs gradually diminished within a fortnight, and he was discharged from the hospital with few symptoms. One month later, he did not complain about diplopia but about fatiguability; the remaining signs were paresis of convergence and weakness of the right superior rectus muscle.

There is little doubt that this transient illness was due to a lesion in the mesencephalic tegmentum, probably ischemic. The analogy with experimental lesions in monkeys was striking, apart from ipsilateral miosis instead of pupillary dilation (central Horner syndrome?) and the marked hypotonia of the left side of the face and the left arm, with slight facial weakness. The latter findings suggest a more ventral extension of the lesion, beyond the tegmental area.

In addition, the residual signs suggest that the third nerve nuclei were not quite spared. The most unexpected features were the difficulty in locating the left arm, but only on the left side of the body, and the circumambulation to the left. These could not be ascribed to a vestibular or cortical dysfunction, and must represent a defect of visuospatial orientation at a mesencephalic level.

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Physiological Aspects of Visual Perception

To the Editor.—Dr Denny-Brown's highly personal view of the primate visual system as propounded in his Bennett lecture (*Arch Neurol* 33:219, 1976) is sufficiently at variance with other work in the field that some comment is necessary. The division of visual perception into object vision-vision for cognitive detail-and panoramic vision-vision for spatial localization and behavioral import-is heuristically useful, and has been discussed in detail.[1] However, the bulk of behavioral and physiological evidence must assign the superior colliculus to participation in "panoramic" rather than "object" vision.

Dr Denny-Brown's arguments hinge on the drastic effects of collicular ablation in his hands. He argues that "complete removal of the superior colliculus resulted in the same loss of visual object identification, binocular fixation, and visuosocial behavior that followed removal of area 17." Most other investigators have failed to show such dramatic deficits from collicular ablation. Thus, Rosvold et al[2] showed that monkeys with collicular lesions had no difficulty in performing discriminations difficult for animals with striate lesions. Pasik et al[3] showed that monkeys with collicular ablations had a full range of optokinetic and vestibular eye movements.

Where visual deficits have been shown in the presence of collicular ablations, special methods of testing have been necessary to elicit them. Anderson and Symmes[4] showed that monkeys with bilateral collicular lesions could easily discriminate stationary patterns or still patterns from moving patterns, but could not discriminate between rates of movement of briefly presented stimuli. Wurtz and Goldberg[5] showed that animals with total unilateral collicular lesions could quite accurately locate stimuli in the contralateral visual field, but had an increased latency of onset of eye movement to fixate such stimuli. Keating[6] showed that monkeys with bilateral collicular lesions have a slight difficulty locating very briefly flashed peripheral stimuli. No other workers either before or after Dr Denny-Brown's original report[7] have been able to describe anything like the blindness he described after collicular lesions. Instead, the above studies all show that monkeys without the superior colliculus have difficulty-but not total impairment-in noticing, locating, and reacting to peripheral stimuli. In other words, monkeys with collicular lesions have a subtle deficit in "panoramic" vision.

Insofar as one can generalize from the results of single neuron studies, the properties of collicular and striate neurons also support the thesis that the colliculus is more important in "panoramic" than "object" vision. Hubel and Wiesel[8] showed that most single neurons in monkey striate cortex have small receptive fields and are specific for stimulus parameters such as orientation, color, direction of movement, and stimulus shape. Cells in the superior colliculus have much larger receptive fields and are for the most part indifferent to stimulus parameters.[9,10] Many cells in the superficial layers of the superior colliculus have an enhenced response to stimuli that will become the targets of saccadic eye movements, a property that suggests that the colliculus participates in the process of shifting gaze to the periphery.[11] All these data support the contention that, unlike the striate cortex, the superior colliculus subsumes "panoramic" vision.

Although Dr Denny-Brown's view that vision has an object component and a panoramic component is most likely correct, his contention that the superior colliculus provides a significant contribution to object vision but not to panoramic vision is not supported by the mass of physiological and behavioral evidence from other laboratories.

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1. Schneider GE: Two visual systems. *Science* 163:895-982, 1969.
2. Rosvold HE, Mishkin M, Szwarzbart MK: Effects of subcortical lesions in monkeys on visual discrimination and single alternation performance. *J Comp Physiol Psychol* 51:437-444, 1958.
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Effects of lesions on eye movements. *J Neurophysiol* 35:587-596, 1972.

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10. Cynader M, Berman N: Receptive-field organization of monkey superior colliculus. *J Neurophysiol* 35:187-201, 1972.

11. Goldberg ME, Wurtz RH: Activity of superior colliculus in behaving monkeys: II. Effect of attention on neuronal responses. *J Neurophysiol* 35:560-574, 1972.

In Reply.—Dr Goldberg makes many erroneous statements. We did not describe "blindness after collicular lesion" either in 1962 or in 1976. We were interested in the nature of the response to visual stimulus remaining after recovery from bilateral complete ablation of the superior colliculus. We carefully described the great facilitation of visual identification of still objects if a small rostral fragment of one colliculus, with its related corticomesencephalic fibers, remained intact. The lesions described by Pasik et al were incomplete, and this crucial area is not illustrated in their charts. Those of Rosvold et al spared this area, and those of Anderson and Symmes spare its lateral part, even in their most severe lesion.

The remarkable defect in perception in the immediate postoperative period that we described was also noted by Anderson and Symmes, and in their most complete animal by Pasik et al. Dr Goldberg should also read those articles that he quotes. He seems unaware of the inconsistency of his statements. If, as he says, vision is not significantly affected by complete removal of colliculus, how can he also conclude that the colliculus "subserves panoramic vision"?

We are unable to understand how Dr Goldberg can conclude that the responses that he has observed in single colliculus neurons belong to visual awareness, and not, for example, to part of a reflex mechanism for convergence fixation.

We have demonstrated to our own satisfaction, if not to Dr Goldberg's, that the monkey can make a visually directed reaching response to a moving object in the peripheral field in the complete absence of both superior colliculi, and that such response fails as a result of a very limited bilateral lesion in the tegmentum in the presence of intact colliculi. These findings, repeated many times, should speak for themselves.

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Prevalence and Malignancy of Alzheimer Disease

To the Editor.—In the April issue of the Archives (33:217, 1976), two items of interest warrant comment. These pertain to the prevalence and malignancy of Alzheimer disease (AD) reported by Katzman and his associates.

We agree that AD is certainly malignant in that its course is relentless and eventually terminates in death. We also agree that in patients with AD who through inanition become vulnerable to intercurrent infections, the primary diagnosis of AD should be made in pathologically proved instances. We believe that the clinical course of AD is so characteristic that if the patients are periodically examined at about six-month intervals, preferably by the same physician, no special "neuropsychological" tests are necessary to establish the clinical diagnosis. It should be borne in mind, however, that the progressive deterioration is quite similar to that of Pick disease and progressive subcortical gliosis, so that definitive diagnosis still must be determined by microscopic study.

One of us has continued to investigate all brains of patients coming to autopsy at St. Elizabeths Hospital of many years; a silver stain (Bodian) is performed on every brain, irrespective of the psychiatric diagnosis. We reported on the indicence of AD and other cerebral conditions over a 15-year interval at the Seventh International Congress of Neuropathology, held in Budapest in 1974. There were 2,804 autopsies; the clinical history was personally reviewed before brain dissection in every case. Based on our unitary concept of Alzheimer disease, the frequency of this syndrome was 16.4%. The ages on admission ranged from 46 to 94 years, with an average of 73.5; the ages at death varied from 49 to 100 years, with a mean of 76.46.

Our studies also showed that 83.6% of the elderly patients did not have evidence of a definite cerebral degenerative disease. Clinically, these patients did not show the restless activity so characteristic of AD; their speech was adequate and they generally recalled events of their early life, but might have disturbances of recent memory. These patients had no significant number of widely disseminated argyrophilic plaques or neurofibrillary tangles. The classification of "senile dementia" should be reserved for this class of patients. We have studied the brains of patients over 90 years of age, and even a few above 100 years of age, at death and found no evidence of argyrophilic plaques in the silver preparations. Because of this finding it seems to us advisable to discontinue the use of the term "senile" plaque; they are not a universal accompaniment of increased age.

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Myoclonus and Alzheimer Disease

To the Editor.—Faden and Towsend, in the April issue of the Archives (33:278, 1976), consider myoclonus a confusing sign in early differential diagnosis of Alzheimer and Crutzfeld-Jakob diseases. They overlooked our own publication (*Neurology* 13:811-823, 1963) in which we called attention to the association between myoclonus and Alzheimer disease. The observation of neurofibrillary tangles in the anterior horn cells in such cases suggests that the myoclonus may arise in the spinal cord, as well as in the cerebrum. In addition, the appearance of myoclonus probably depends on the rate of progression and eventual distribution of neuronal degeneration, rather than the disease process.

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In Reply.—There have been at least six reports in addition to the one by Feldman et al[1] that describe myoclonus in conjunction with *familial* Alzheimer disease. These are reviewed in Jacob's article,[2] which is cited in our article. We did not include any of these references, since the article dealt specifically with "sporadic, nonfamilial" cases of Alzheimer disease, ie, those that could be confused with Creutzfeld-Jacob disease. One reference[3] describing myoclonus in nonfamilial Alzheimer disease was omitted, however, and was recently brought to my attention.

The familial cases described by Feldman et al also showed prominent extrapyramidal signs as well as generalized seizures. Thus, their finding of neurofibrillary tangles in the anterior horn cells in this family would seem to be of uncertain significance in implicating a spinal cord origin of the myoclonus in sporadic cases of Alzheimer disease.

Since the myoclonus in Alzheimer disease has been described as both an early and a late manifestation of the disease process, the rate of progression of the disease does not seem to be a critical factor in the appearance of the myoclonus. Moreover, while the degree or distribution of the neuronal degeneration may be important factors, this has not been demonstrated.

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1. Feldman RG, Chandler KA, Levy LL, et al: Familial Alzheimer's disease. *Neurology* 33:811-823, 1963.

2. Jacob H: Muscular twitching in Alzheimer's disease, in Walstenholme GEW, O'Conner M (eds): *Alzheimer Disease and Related Conditions.* London, J & A Churchill Ltd, 1970, pp 75-93.

3. Chokroverty S: Alzheimer's disease, in *Proceedings of the Weekly Seminar in Neurology.* Hines, Ill, Edward Hines, Jr, Veterans Administration Hospital, vol 17, 1967.

Aluminum and Alzheimer Disease

To the Editor.—I read with interest the editorial on Alzheimer disease by Katzman in the April issue of the Archives (33:217, 1976). A colleague and I[1] recently reported localization of aluminum and silicon in senile plaques in six patients with Alzheimer disease by using a Castaing electron microprobe. We did not identify aluminum in the comparatively few neurofibrillary tangles available for examination. Crapper et al[2] studied with an atomic absorption spectrophotometer the amount of aluminum in samples of brain from 18 patients with Alzheimer disease. This technique measures the total aluminum concentration in a given brain sample. In two of their cases these authors reported a significant association between abnormal quantities of aluminum and neurofibrillary tangles, but not of senile plaques. This was surprising because the tissue in question apparently contained both senile plaques and tangles. Terry and Pena,[3] using an electron microprobe, were unable to localize aluminum in human neurofibrillary tangles, but found it in "the area of" neurofibrillary tangles in rabbits intoxicated experimentally with aluminum phosphate. The discrepancy between our findings and those of Crapper et al could possibly be explained by the inability of the electron microprobe to identify aluminum in neurofibrillary tangles, perhaps because such small quantities are below the level of sensitivity of the instrument.

These discrepancies will be resolved, presumably, but the fact remains that there appears to be too much aluminum in the brains and cerebrospinal fluid[4] of patients with Alzheimer disease.

Since aluminum and silicon constitute 74.46% of the elements in the earth's crust, and 33.26% in order of abundance in the lithosphere, hydrosphere, and atmosphere (oxygen, 49.52%),[5] there is no doubt that human beings are exposed to these elements. Would it be too audacious to consider that the presence of tangles and plaques in the brain in that nebulous entity referred to as Alzheimer disease is the result of an aluminum intoxication, possibly exogenous and possibly sensitive to chelators?

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1. Duckett S, Galle P: Mise en évidence de l'aluminium dans les plaques séniles de la maladie d'Alzheimer: Étude à la microsonde de Castaing. *C R Acad Sci* 282:393, 1976.
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Benzodiazepine Anticonvulsant

To the Editor.—The following sentence in Brown's article (*Arch Neurol* 33:326, 1976) appears to be confusing and misleading, and requires clarification: "The drug (clonazepam) is not approved by the FDA for treatment of grand mal, partial seizures with complex symptoms (psychomotor, temporal lobe), or focal seizures." This statement provoked a number of physicians to contact us as to whether or not they can "legally" prescribe clonazepam to patients with "mixed epilepsy" (petit mal and grand mal; myoclonic and grand mal). We do not believe that Dr Browne intended to advise physicians against the use of clonazepam in patients with grand mal and an "approved" type of seizure, but simply meant that the efficacy of clonazepam in the treatment of grand mal epilepsy has not been established in this country.

Browne states, "... no cases of serious hematopoietic, hepatic, or renal toxicity appear to have occurred." We are cognizant of two reports[1,2] of thrombocytopenia in association with clonazepam therapy, one of which stated that nine of 26 patients experienced a decrease in the thrombocyte count while receiving only clonazepam.[1]

More important is that our experience with clonazepam in 42 patients over a period of approximately two years has been disappointing. We have found the drug ineffective in controlling major motor (grand mal), true petit mal, and psychomotor (temporal lobe) seizures. Of four patients with infantile myoclonic attacks (infantile spasms, hypsarrhythmia), one was controlled and three derived no benefit from clonazepam therapy. Six of 28 older children with myoclonic epilepsy (atypical petit mal, Lennox-Gastaut syndrome, petit mal variant) experienced a temporary reduction in the frequency of seizures, but the remaining 22 children did not respond to treatment with this drug.

We were compelled to discontinue clonazepam in 25 patients because of one or more of the following untoward reactions: severe drowsiness, lethargy, marked ataxia, pronounced mental dullness, drastic changes in personality, or serious behavioral problems. Marked drowsiness, lethargy, ataxia, and mental obtuseness occurred individually or in combination in association with relatively small doses of clonazepam in most patients. An increase in the frequency of grand mal convulsions occurred in two patients during clonazepam therapy, and one child experienced his initial major motor convulsion while being treated with this drug.

Our experience indicates that clonazepam is less effective than diazepam (Valium) in the treatment of childhood myoclonic epileptic seizures when the latter drug is administered in proper dosage every three hours.[3] Moreover, we have found clonazepam to be much more toxic than diazepam. We have had approximately 40 years experience with the use of 4:1 ketogenic diet regimen in the treatment of childhood myoclonic seizures, which is the major indication for usage of clonazepam, and have consistently found it to be the most efficacious form of therapy for this type of epilepsy.[3] Some of our patients who did not respond to clonazepam therapy were subsequently controlled by the ketogenic diet.

S. Livingston, MD
L. L. Pauli, MD
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1. Girke W, Krebs FA, Lenzner W: Esultate mit einen neuen Antikonvulsivum: Neuentwicklung eines Medikaments aus der Diazepamreihe. *Arztliche Praxis* 25:4518, 4520, 4522, 1973.
2. Veall RM, Hogarth HC: Thrombocytopenia during treatment with clonazepam. *Br Med J* 2:462, 1975.
3. Livingston S: *Comprehensive Management of Epilepsy in Infancy, Childhood and Adolescence.* Springfield, Ill, Charles C Thomas Publisher, 1972.

In Reply.—I did not intend to advise against the use of clonazepam in patients with tonic-clonic ("grand mal") and an "approved" type of seizure, and I thank Drs Livingston and Pauli for making this clarification. I also have found clonazepam to be ineffective in controlling tonic-clonic seizures and partial seizures with complex symptoms, although some workers report favorable results.

I must disagree, however, with the statement that clonazepam is "ineffective" for absence ("true petit mal") seizures. Double-blind studies performed by Chandra[1] and being performed by the National Institutes of Health[2] have demonstrated significant reductions in absence seizure frequency and occurrence of 3 hz spike-wave with clonazepam. In addition, there are over 30 uncontrolled studies in the literature that report largely favorable results.

The high frequency of side effects with clonazepam described by Livingston and Pauli is similar to my earlier experience and the results of early published trials. With newer dosage regimens, the drug is begun at lower doses and increased in dosage more gradually. With these regimens the incidence of side effects with clonazepam, while considerable, has not been as great as Livingston and Pauli report.

The article by Girke et al on thrombocytopenia in association with clonazepam did not appear in my review because it was published in a journal that is not included in the data base for Medlars searches. The article by Veal and Hogarth appeared after my review had been submitted. Livingston and Pauli are, of course, correct in calling attention to this reported complication of clonazepam. However, it would be misleading to leave the impression that serious thrombocytopenia is an established or common side effect of clonazepam. The lowest level of thrombocytopenia in Girke et al's nine patients was 90,000/cu mm, and the thrombocytopenia reversed in every case. It is not stated if this reversal occurred while patients were taking clonazepam or after the drug had been removed. The patient reported by Veall and Hogarth was begun on phenytoin the month before she was begun on clonazepam, and it is impossible to determine which, if either, drug was responsible for the observed thrombocytopenia. Hoffman-La Roche Inc has data on file (P.D. Cohn, MD, written communication, June 24, 1976) for over 900 patients in the United States who took clonazepam, and 85 of these patients had serial platelet counts performed. Only two patients ever had platelet counts below 100,000/cu mm. The first patient had a count of 90,000/cu mm, which returned to normal levels while the patient continued to take clonazepam. The second patient was taking multiple drugs and has a history of intermittent thrombocytopenia before, during, and after clonazepam therapy.

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1. Chandra B: Clonazepam in the treatment of petit mal. *Asian J Med* 9:433-435, 1973.
2. Dreiffuss FE, Penry JK, Rose SW, et al: Serum clonazepam concentrations in children with absence seizures. *Neurology* 25:255-258, 1975.

News and Comment

CALENDAR OF MEETINGS

Year	Month	Dates	Meeting
1976	Oct	11-15	European Seminar on Computerized Axial Tomography in Clinical Practice, London
		28-30	Child Neurology Society, annual meeting, Monterey, Calif
1977	July	18-23	27th International Congress of Physiological Sciences, Paris

European Seminar on Computerized Axial Tomography in Clinical Practice.—The first European seminar on the clinical application of computerized axial tomography (EMI scanning) will be held in London, Oct 11 through 15, 1976. The faculty will be drawn mainly from the principal European centers engaged in the use and development of this technique. The emphasis will be on clinicoradiological collaboration, and although most of the speakers will deal with craniocerebral scanning, up to 1½ days will be devoted to whole-body examination methods.

Full details of the program and registration arrangements can be obtained from I. F. Moseley, MD, Lysholm Radiological Department, National Hospital for Nervous Diseases, Queen Square, London WC1.

Annual Meeting of Child Neurology Society.—The fifth annual meeting of the Child Neurology Society will be held in Monterey, Calif, Oct 28 through 30, 1976. The meeting is open to all physicians. Registration information and abstract forms may be obtained from the Child Neurology Society, Box 486 Mayo, 412 SE Union, Minneapolis, MN 55455.

Twenty-seventh International Congress of Physiological Sciences.—This congress, to be held July 18 through 23, 1977, in Paris, will be divided into two successive parts. The first two days will be devoted to general lectures; during the last four days, specialized meetings (symposia, free communications, and posters), each representing a different field of the physiological sciences, will take place.

Further information may be obtained by writing Prof J. Scherrer, Secrétariat du XXVIIe Congrès International des Sciences Physiologiques, U. E. R. Pitié-Salpêtrière, Cedex 1300, R-75300 Paris, France.

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edited by
Seymour Diamond, M.D.
Director of the Diamond
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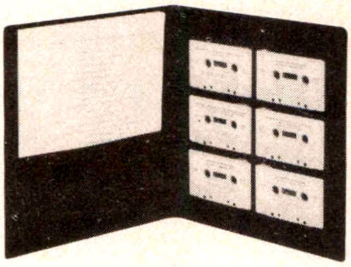

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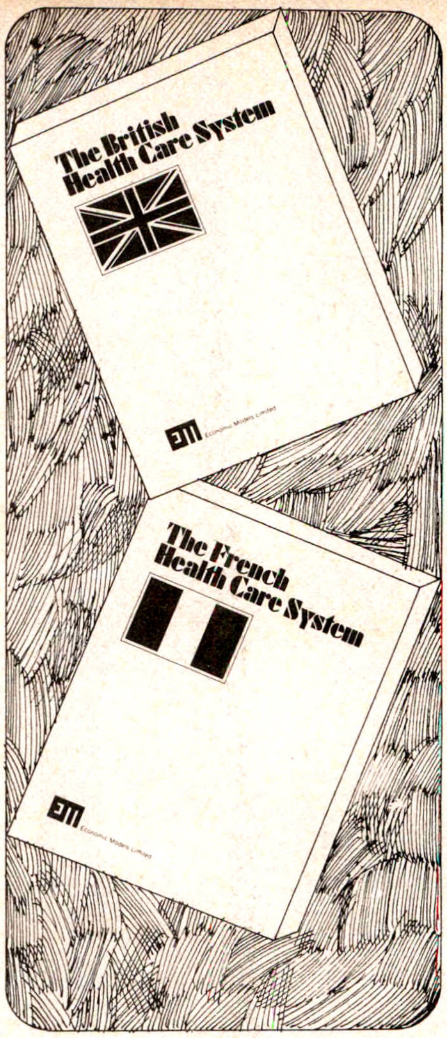
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Britain's health care system is predominantly nationalized. France offers its citizens a national health and social insurance plan. These comprehensive references cover each system's evolution...operation...application...problems...achievements...and personnel.

Both books will be available Fall, 1976. **The French Health Care System** (OP-460) costs $3.50; **The British Health Care System** (OP-461), $7.50. The set is $10. To order your copies, write **Order Dept., AMA, 535 N. Dearborn St., Chicago, Ill. 60610.**

Your parkinsonian patients live in a world of "obstacles"

Posed by professional model.

Sinemet®

a combination of carbidopa and levodopa

can mean a world of difference for some parkinsonian patients

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See last page of advertisement for brief summary of prescribing information.

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Symptomatic relief

SINEMET usually relieves the major symptoms of Parkinson's disease:

- **rigidity**
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Improved performance of daily activities

Symptomatic relief of Parkinson's disease may enable some patients to carry out such routine daily activities as:

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- **dressing**
- **eating**
- **maintaining personal hygiene**

SINEMET is contraindicated in:

- Patients receiving monoamine oxidase inhibitors. These inhibitors must be discontinued at least two weeks prior to initiating therapy with SINEMET.
- Patients with known hypersensitivity to this drug.
- Patients with narrow-angle glaucoma. (Patients with chronic wide-angle glaucoma may be treated cautiously if intraocular pressure is well controlled and the patient is monitored carefully for changes in intraocular pressure during therapy.)
- Patients with suspicious, undiagnosed skin lesions or a history of melanoma. Because levodopa may activate a malignant melanoma, SINEMET should not be used in these patients.

All cautionary information with levodopa also applies to SINEMET. Turn to the back page for additional information.

Sinemet®

a combination of carbidopa and levodopa

can mean a world of difference for some parkinsonian patients

When SINEMET is to be given to patients who are being treated with levodopa, levodopa must be discontinued at least 8 hours before therapy with SINEMET is started. In order to reduce adverse reactions, it is necessary to individualize therapy. See the Warnings (below) and Dosage and Administration sections in the full prescribing information before initiating therapy.

Contraindications: MAO inhibitors and SINEMET should not be given concomitantly. MAO inhibitors must be discontinued at least 2 weeks prior to initiating therapy with SINEMET.

SINEMET is contraindicated in patients with known hypersensitivity to this drug and in narrow-angle glaucoma.

Because levodopa may activate a malignant melanoma, it should not be used in patients with suspicious, undiagnosed skin lesions or history of melanoma.

Warnings: Levodopa must be discontinued at least 8 hours before SINEMET is started. SINEMET should be substituted at a dosage that will provide approximately 25 percent of the previous levodopa dosage. (See Dosage and Administration section of full prescribing information.) Patients taking SINEMET should be instructed not to take additional levodopa unless prescribed.

As with levodopa, SINEMET may cause involuntary movements and mental disturbances. These reactions may be due to increased brain dopamine following administration of levodopa. All patients should be observed carefully for development of depression with concomitant suicidal tendencies. Treat with caution patients with past or current psychoses. *Because carbidopa permits more levodopa to reach the brain and, thus, more dopamine to be formed, dyskinesias may occur at lower dosages and sooner with SINEMET than with levodopa.* Occurrence of dyskinesias may require dosage reduction.

SINEMET should be administered cautiously to patients with severe cardiovascular or pulmonary disease, bronchial asthma, renal, hepatic or endocrine disease.

Exercise care in administering SINEMET, as with levodopa, to patients with history of myocardial infarction who have residual atrial, nodal, or ventricular arrhythmias. In such patients, cardiac function should be monitored with particular care during period of initial dosage adjustment, in a facility with provisions for intensive cardiac care.

As with levodopa, there is possibility of upper G.I. hemorrhage in patients with history of peptic ulcer.

Usage in Pregnancy and Lactation: Although effects of SINEMET on human pregnancy and lactation are unknown, both levodopa and combinations of carbidopa and levodopa have caused visceral and skeletal malformations in rabbits. Use of SINEMET in women of childbearing potential requires that anticipated benefits of the drug be weighed against possible hazards to mother and child. SINEMET should not be given to nursing mothers.

Usage in Children: Safety of SINEMET in patients under 18 has not been established.

Precautions: As with levodopa, periodic evaluations of hepatic, hematopoietic, cardiovascular, and renal function are recommended during extended therapy.

Patients with chronic wide-angle glaucoma may be treated cautiously with SINEMET provided intraocular pressure is well controlled and patient is monitored carefully for changes in intraocular pressure during therapy.

Symptomatic postural hypotension can occur. For this reason, SINEMET should be given cautiously to patients on antihypertensive drugs. When SINEMET is started, dosage adjustment of the antihypertensive drug may be required. (For patients receiving pargyline, see the contraindication on MAO inhibitors.)

Since phenothiazines and butyrophenones may reduce therapeutic effects of levodopa, they should be administered with caution if concomitant administration with SINEMET is necessary, and patients should be carefully observed for loss of antiparkinsonian effect.

Adverse Reactions: Most common serious adverse reactions occurring with SINEMET are choreiform, dystonic, and other involuntary movements. Other serious adverse reactions are mental changes including paranoid ideation and psychotic episodes, depression with or without development of suicidal tendencies, and dementia. Convulsions also have occurred; however, a causal relationship with SINEMET has not been established.

A common but less serious effect is nausea.

Less frequent adverse reactions are cardiac irregularities and/or palpitations, orthostatic hypotensive episodes, bradykinetic episodes (the "on-off" phenomenon), anorexia, vomiting, and dizziness.

Rarely, G.I. bleeding, development of duodenal ulcer, hypertension, phlebitis, hemolytic anemia, leukopenia, and agranulocytosis have occurred.

Other adverse reactions reported with levodopa include dry mouth, dysphagia, sialorrhea, abdominal pain and distress, ataxia, increased hand tremor, headache, numbness, weakness and faintness, bruxism, confusion, insomnia and nightmares, hallucinations and delusions, agitation and anxiety, malaise, fatigue, euphoria, muscle twitching and blepharospasm (may be taken as an early sign of excess dosage; consider dosage reduction at this time), trismus, burning sensation of tongue, bitter taste, diarrhea, constipation, flatulence, flushing, skin rash, increased sweating, bizarre breathing patterns, urinary retention, urinary incontinence, diplopia, blurred vision, dilated pupils, hot flashes, weight gain or loss, dark sweat and/or urine, oculogyric crises, sense of stimulation, hiccups, edema, loss of hair, hoarseness, priapism, and activation of latent Horner's syndrome.

Abnormalities in laboratory tests may include elevations of blood urea nitrogen, SGOT, SGPT, lactic dehydrogenase, bilirubin, alkaline phosphatase, protein-bound iodine, and positive Coombs test. More commonly, levels of blood urea nitrogen, creatinine, and uric acid are lower during administration of SINEMET than with levodopa.

Overdosage: Management of acute overdosage with SINEMET is basically the same as management of acute overdosage with levodopa; however, pyridoxine is not effective in reversing the actions of SINEMET.

How Supplied: Tablets SINEMET-10/100 and Tablets SINEMET-25/250 are supplied in bottles of 100.

For more detailed information, consult your MSD representative or see full prescribing information, Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486

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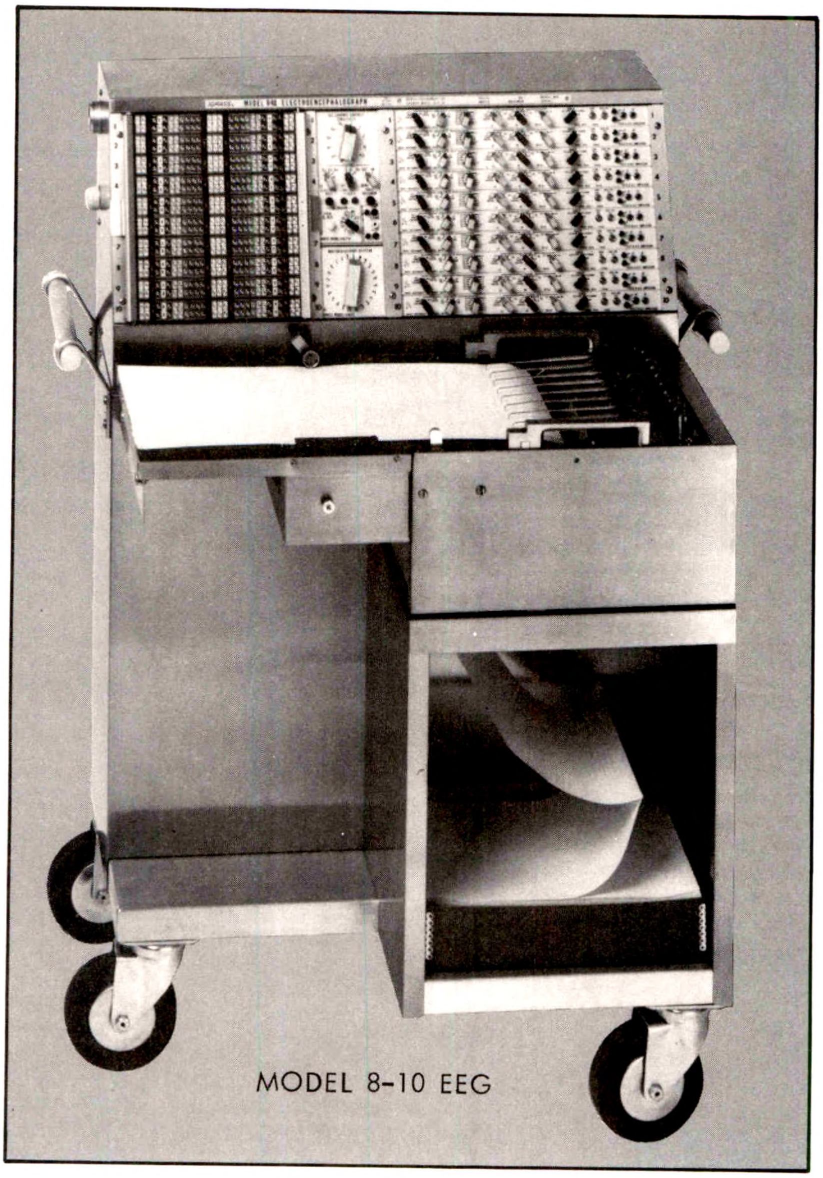

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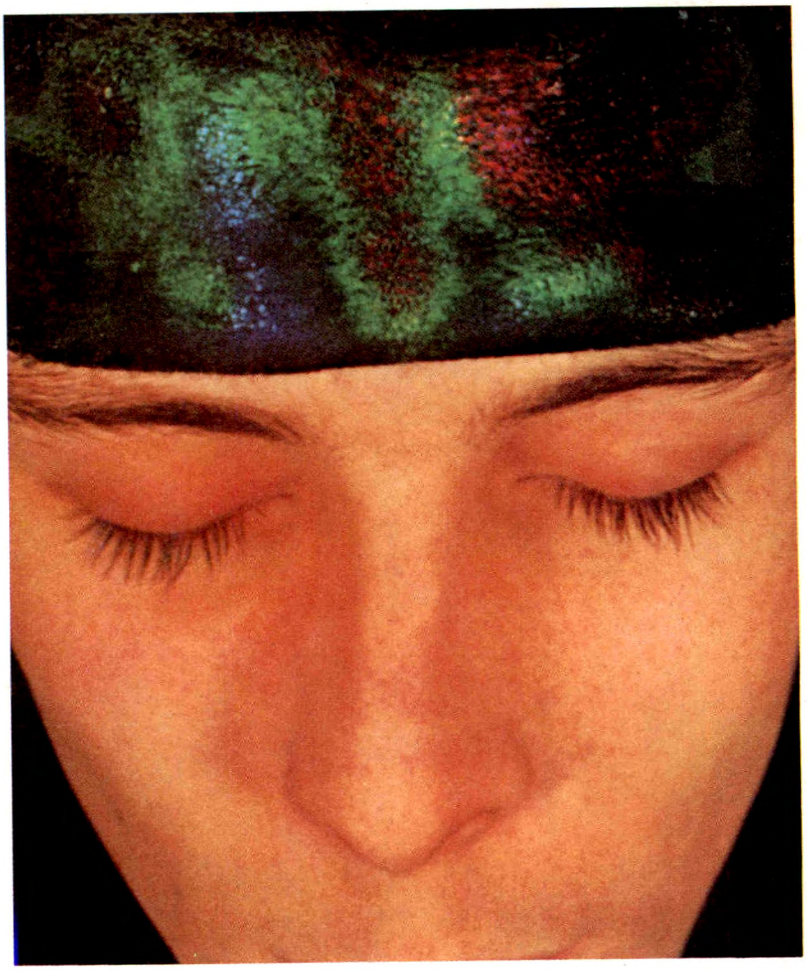
seeing migraine headache in its "true colors"



Specific vascular changes are revealed by liquid crystalography

Liquid crystal thermography dynamically demonstrates the unilateral surface temperature changes reflective of the dilation of deep cerebral arteries during a migraine attack. Liquid crystals allow differences in skin temperature to be "mapped" directly on the subject. Variations in skin heat loss are registered immediately, enabling rapid temperature changes to be followed easily. (Red reflects the coolest temperature, then green, blue, and violet.)

This picture was taken of a migraine sufferer during an attack. The colors over the left eye reflect the cooler skin temperature due to the unilateral decreased blood flow to the forehead skin vessels that results from dilation of cerebral vessels on the affected side.

Specific therapy for migraine complicated by tension and G.I. upset

The combined vasoconstrictive actions of ergotamine and caffeine offer the best therapeutic results in helping to abort or relieve the migraine headache. Additionally, belladonna alkaloids help relieve the accompanying gastrointestinal irritability. And the patient's nervous tension, perhaps a precipitating factor in the onset of an attack, is often allayed by the pentobarbital in Cafergot P-B.

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SUPPOSITORIES: Gynergen® (ergotamine tartrate, U.S.P.) 2 mg.; caffeine, U.S.P., 100 mg.; Bellafoline® (levorotatory alkaloids of belladonna, as malates) 0.25 mg.; pentobarbital, N.F., (*Warning:* May be habit forming) 60 mg.; inactive ingredients: tartaric acid, N.F., malic acid, lactose, U.S.P., and theobroma oil, U.S.P.

Contraindications: Peripheral vascular disease, coronary heart disease, hypertension, impaired hepatic or renal function, sepsis, and pregnancy. Hypersensitivity to any of the components.

Precautions: Although signs and symptoms of ergotism rarely develop even after long term intermittent use of the orally or rectally administered drugs, care should be exercised to remain within the limits of recommended dosage.

Adverse Reactions: Numbness and tingling of fingers and toes, muscle pains in the extremities, weakness in the legs, precordial distress and pain, transient tachycardia or bradycardia, nausea, vomiting, localized edema, and itching. Drowsiness may occur with Cafergot P-B.

Adult Dosage: *Orally*—Two tablets at first sign of attack; if needed, 1 additional tablet every half hour until relieved (maximum, 6 per attack or 10 per week). *Rectally*—One suppository as early as possible in attack; second in 1 hour, if needed (maximum, 2 per attack or 5 per week).

Overdosage: Symptoms include vomiting; numbness, tingling, pain and cyanosis of the extremities associated with diminished or absent peripheral pulses; hypertension or hypotension; drowsiness, stupor, coma, convulsions and shock. A case has been reported of reversible bilateral papillitis with ring scotomata in a patient who received five times the recommended daily adult dose over a period of 14 days. Treatment consists of induction of emesis, gastric lavage, and catharsis; maintenance of adequate pulmonary ventilation; correction of hypotension; and control of convulsions. Treatment of peripheral vasospasm should consist of warmth, but not heat, and protection of the ischemic limbs. Vasodilators may be used with benefit but caution must be exercised to avoid aggravating an already existent hypotension.

Before prescribing, see package insert for full product information.

Sandoz Pharmaceuticals, East Hanover, N.J. 07936

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archives of Neurology

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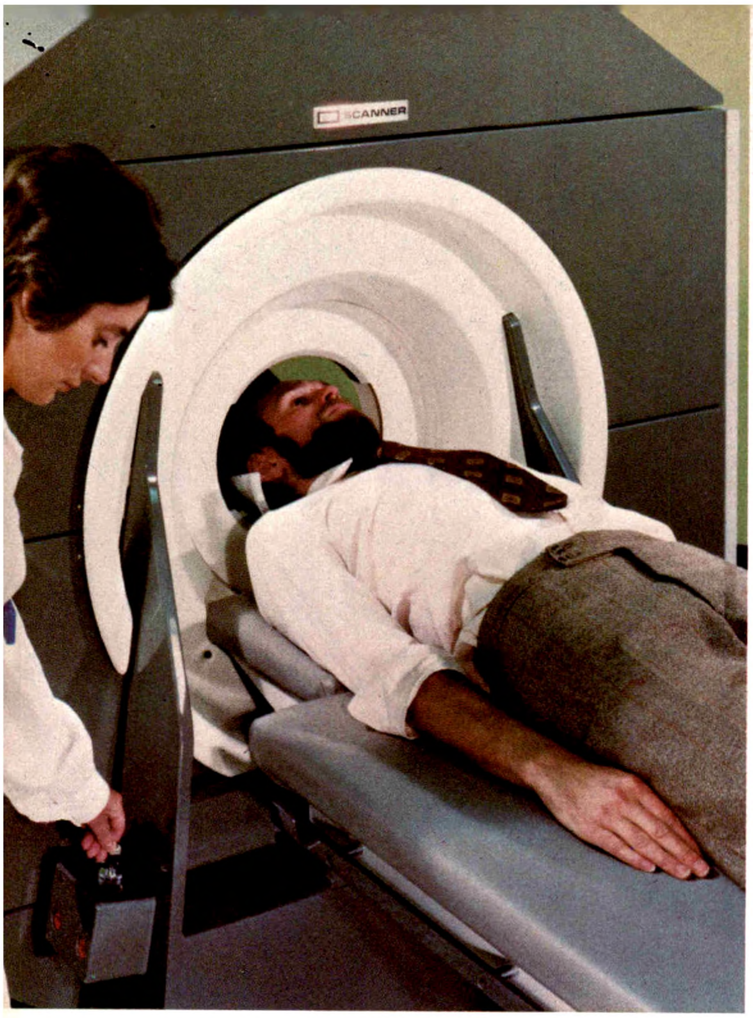

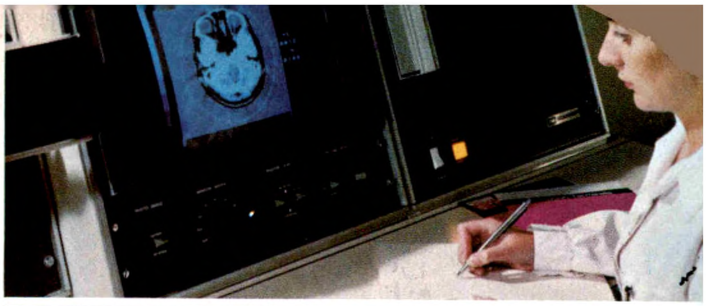

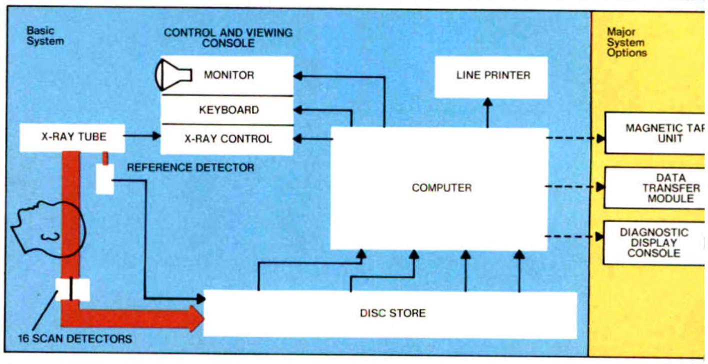

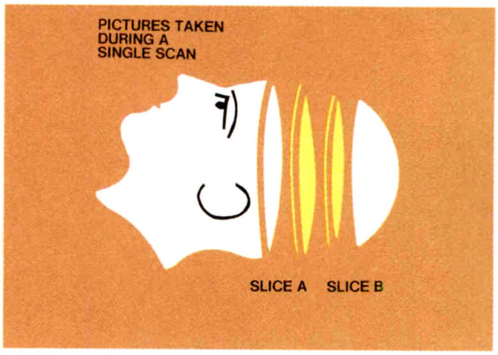
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The fully proven CT system

EMI Medical now offers two computerized tomographic systems based on thoroughly proven EMI technology. For scanning both the head and body, there is the EMI-Scanner CT5005 Advanced General Diagnostic C.T. System. In recognition of the specialized requirements of neuroradiological studies, EMI Medical also offers the EMI-Scanner CT1010 Advanced Neuro C.T. System, designed specifically for institutions whose neurological and neurosurgical case-loads warrant a computerized tomographic system dedicated solely to scanning of the head and upper spinal column. The CT1010 allows high patient throughput and increased clinical flexibility within a significantly more economical system. Obviously, the final test of any CT system is the quantity and quality of the diagnostic information it provides. The EMI-Scanner has met this test in actual diagnostic use in hundreds of institutions. It is the world's only fully proven CT scanner system. For more information on the CT1010 Neuro C.T. System, call us or write.

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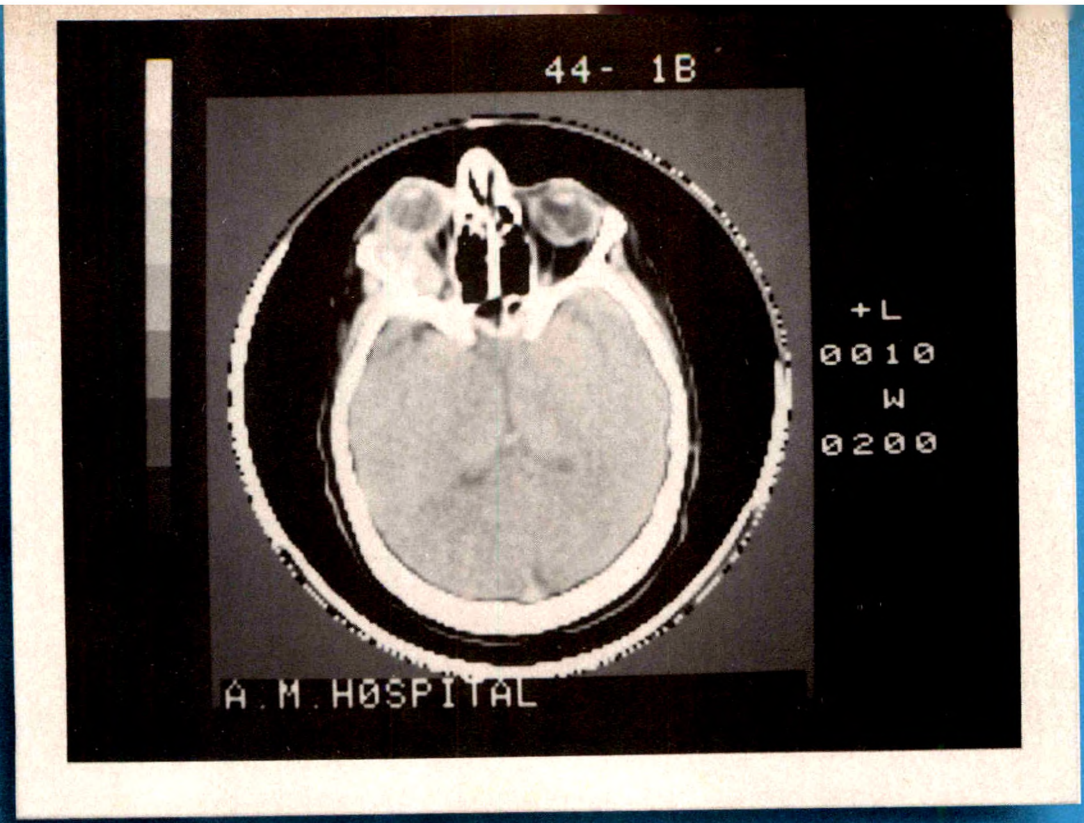

Reproduction of an EMI-SCAN of a young male patient with a 12 month history of increasing proptosis and limitation of lateral occular movements. The scan demonstrates a mass in the lateral section of the left orbit with early calcification visible within the mass. Note the detail visible in the orbital regions.

6-219

Superior diagnostic information in every EMI-SCAN:

The optimal orbital view

The EMI CT1010 Advanced Neuro C.T. System is designed for exclusive use in scanning the head and upper spinal column. The CT1010 provides capability for both standard (180°) and wide (240°) scan angles, the latter being particularly useful in examining patients who may be subject to involuntary head movement. Likewise, standard and high-accuracy scanning speeds are offered. In the high-accuracy mode, the sensitivity of the system is increased by 2½ times. Still greater resolution can be achieved by selecting any section of a scan to be enlarged four times for whole-screen display. An optional clinician's Diagnostic Display Console adds to system flexibility by allowing the viewing of existing results independently of the in-use status of the main scanner installation. For institutions whose case-load warrants a C.T. system dedicated solely to neuroradiological use, the CT1010 allows high patient throughput and increased clinical flexibility within a significantly more economical system. For more information, call us or write.

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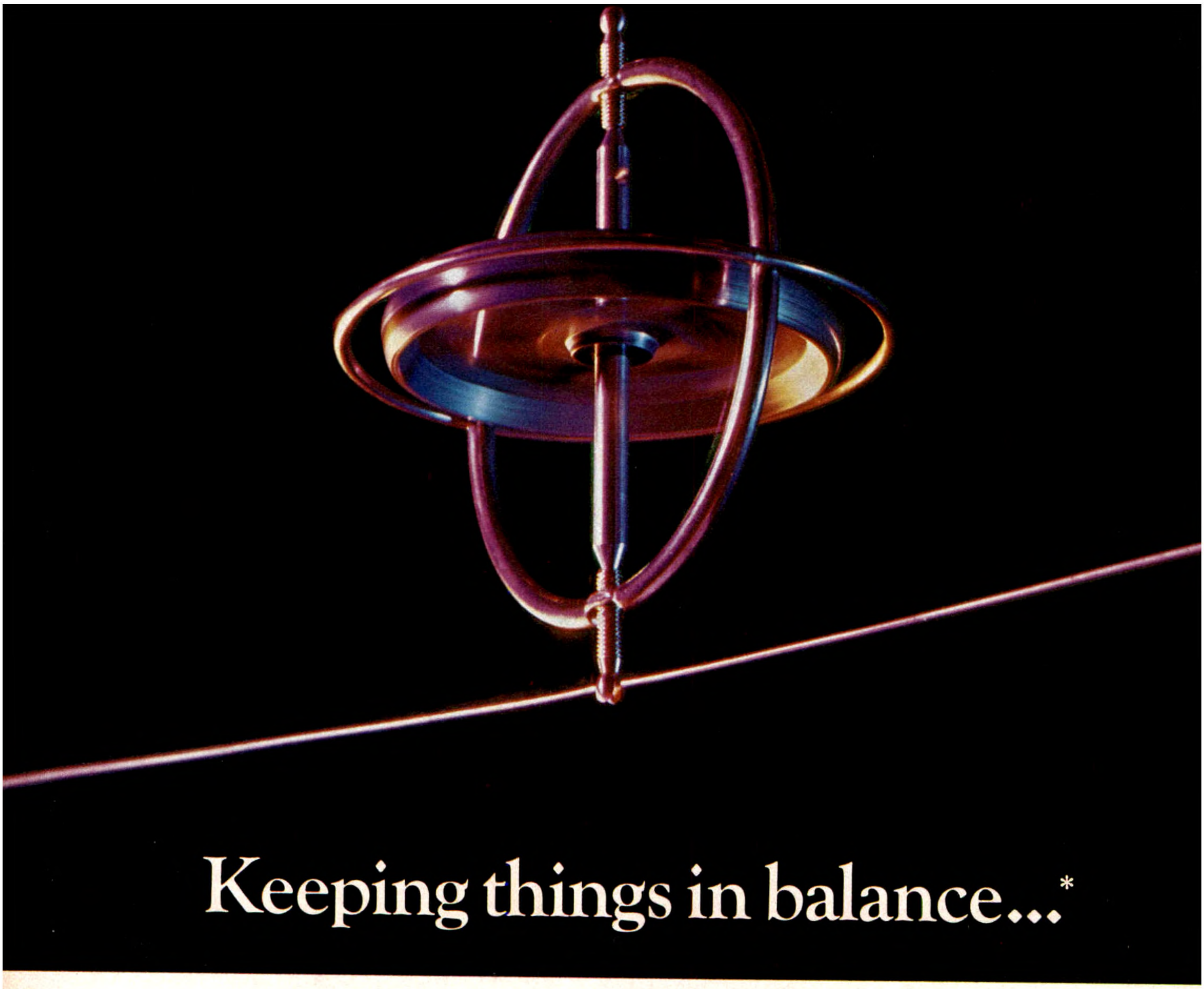

Antivert®/25 Tablets

(25 mg. meclizine HCl)

*INDICATIONS. Based on a review of this drug by the National Academy of Sciences-National Research Council and/or other information, FDA has classified the indications as follows:

Effective: Management of nausea and vomiting and dizziness associated with motion sickness.

Possibly Effective: Management of vertigo associated with diseases affecting the vestibular system.

Final classification of the less than effective indications requires further investigation.

CONTRAINDICATIONS. Administration of Antivert during pregnancy or to women who may become pregnant is contraindicated in view of the teratogenic effect of the drug in rats.

The administration of meclizine to pregnant rats during the 12-15 day of gestation has produced cleft palate in the offspring. Limited studies using doses of over 100 mg./kg./day in rabbits and 10 mg./kg./day in pigs and monkeys did not show cleft palate. Congeners of meclizine have caused cleft palate in species other than the rat.

Meclizine HCl is contraindicated in individuals who have shown a previous hypersensitivity to it.

WARNINGS. Since drowsiness may, on occasion, occur with use of this drug, patients should be warned of this possibility and cautioned against driving a car or operating dangerous machinery.

Usage in Children: Clinical studies establishing safety and effectiveness in children have not been done; therefore, usage is not recommended in the pediatric age group.

Usage in Pregnancy: See "Contraindications."

ADVERSE REACTIONS. Drowsiness, dry mouth and, on rare occasions, blurred vision have been reported.

ROERIG Pfizer

A division of Pfizer Pharmaceuticals
New York, New York 10017

Archives of Neurology VOL 33, NO. 11, NOVEMBER 1976

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By **Gail E. Solomon,** MD, Asst. Prof. of Neurology and Pediatrics, Cornell Univ. Medical College; Director of Electroencephalography, The New York Hospital; and **Fred Plum,** MD, Anne Parrish Titzell Prof. of Neurology, Cornell Univ. Medical College; Neurologist-In-Chief, The New York Hospital. 152 pp. Illustd. Soft cover. $7.50. March 1976. **Order #8495-5.**

DYCK, THOMAS & LAMBERT: Peripheral Neuropathy

Seventy-eight international authorities pool their expertise in this definitive reference. Basic science aspects of pathogenetic mechanisms are exhaustively reviewed through electron microscopy, autoradiography, axonal flow studies and other modes. Material on disease states is equally comprehensive, with clinical signs, differential diagnosis and treatment fully covered.

Edited by **Peter James Dyck,** MD, Mayo Clinic; **P. K. Thomas,** MD, Royal Free Hospital, London; and **Edward H. Lambert,** MD, Mayo Clinic. Two volumes: 1438 pp. 547 ill. plus 3 full-color plates. $120.00. June 1975. **Order #3270/1.**

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The vulnerable ages

The first epileptic seizure is most likely to occur during early childhood and at the onset of puberty

About 9 out of 10 epileptics experience their first seizure before the age of 20—with the highest incidence between 5 and 7, when children start school, and at the onset of puberty, a time of physiological and psychic turmoil.[1] The most common type, grand mal, occurs in approximately 75% of epileptic children,[1] and more than 50% of patients who suffer initially from petit mal develop grand mal seizures before they reach the age of 16.[2]

Mysoline (primidone) for control of grand mal, psychomotor and focal epilepsy

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BRIEF SUMMARY
(For full prescribing information, see package circular.)

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Anticonvulsant

ACTIONS: MYSOLINE acts on the central nervous system to raise seizure threshold or alter seizure pattern. The mechanism(s) of action of anticonvulsant drugs is not known.

Primidone has anticonvulsant activity *per se*. In addition, its two metabolites possess anticonvulsant qualities. The major metabolite is phenylethylmalonamide (PEMA); the other is phenobarbital. In addition to its own anticonvulsant potential, PEMA potentiates phenobarbital.

INDICATIONS: MYSOLINE, either alone or used concomitantly with other anticonvulsants, is indicated in the control of grand mal, psychomotor, and focal epileptic seizures. It may control grand mal seizures refractory to other anticonvulsant therapy.

CONTRAINDICATIONS: Primidone is contraindicated in: 1) patients with porphyria and 2) patients who are hypersensitive to phenobarbital (see ACTIONS).

WARNINGS: The abrupt withdrawal of antiepileptic medication may precipitate status epilepticus.

The therapeutic efficacy of a dosage regimen takes several days before it can be assessed.

Use in pregnancy: Recent reports strongly suggest an association between the use of anticonvulsant drugs by women with epilepsy and an elevated incidence of birth defects in children born to these women. Reference has been made to primidone in several cases in which it was used *in combination* with other anticonvulsants; but its teratogenicity has not been conclusively demonstrated. The possibility exists that other factors, *e.g.*, genetic factors or the epileptic condition, may contribute to the higher incidence of birth defects. The data also indicate that the great majority of mothers receiving anticonvulsant medication deliver normal infants.

Anticonvulsant drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and risk to both mother and the unborn child.

When the nature, frequency, and severity of the seizures do not pose a clear threat to the patient, good medical practice requires that the physician weigh the expected therapeutic benefit of anticonvulsant therapy against possible risk on an individual basis.

Neonatal hemorrhage, with a coagulation defect resembling vitamin K deficiency, has been described in newborns whose mothers were taking primidone and other anticonvulsants. Pregnant women under anticonvulsant therapy should receive prophylactic vitamin K_1 therapy for one month prior to, and during, delivery.

The physician should weigh all of the foregoing considerations when treating and counseling epileptic women of childbearing potential.

PRECAUTIONS: The total daily dosage should not exceed 2 Gm. Since MYSOLINE therapy generally extends over prolonged periods, a complete blood count and a sequential multiple analysis-12 (SMA-12) test should be made every six months.

In nursing mothers: There is evidence that in mothers treated with primidone, the drug appears in the milk in substantial quantities. Since tests for the presence of primidone in biological fluids are too complex to be carried out in the average clinical laboratory, it is suggested that the presence of undue somnolence and drowsiness in nursing newborns of MYSOLINE-treated mothers be taken as an indication that nursing should be discontinued.

ADVERSE REACTIONS: The most frequently occurring early side effects are ataxia and vertigo. These tend to disappear with continued therapy, or with reduction of initial dosage. Occasionally, the following have been reported: nausea, anorexia, vomiting, fatigue, hyperirritability, emotional disturbances, sexual impotency, diplopia, nystagmus, drowsiness, and morbilliform skin eruptions. Occasionally, persistent or severe side effects may necessitate withdrawal of the drug. Megaloblastic anemia may occur as a rare idiosyncrasy to MYSOLINE and to other anticonvulsants. The anemia responds to folic acid, 15 mg. daily, without necessity of discontinuing medication.

DOSAGE AND ADMINISTRATION: The average adult dose is 0.75 to 1.5 Gm. per day. The initial dose is 250 mg. Increments of 250 mg. are added, usually at weekly intervals, to tolerance, or therapeutic effectiveness, up to daily doses not exceeding 2.0 Gm. A typical dosage schedule for the introduction of MYSOLINE (primidone) is as follows:

Adults and Children Over 8 Years of Age

1st Week 250 mg. daily at bedtime	*2nd Week* 250 mg. b.i.d.
3rd Week 250 mg. t.i.d.	*4th Week* 250 mg. q.i.d.

In children under 8 years of age, maintenance levels are established by a similar schedule, but at one-half the adult dosage. It is best to begin with 125 mg., with gradual weekly increases of 125 mg. a day, to a daily total usually between 500 mg. and 750 mg.

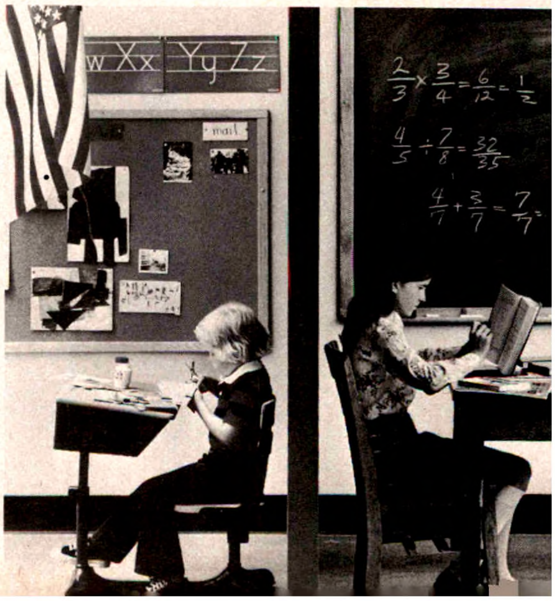
In patients already receiving other anticonvulsants: MYSOLINE should be gradually increased as dosage of the other drug(s) is maintained or gradually decreased. This regimen should be continued until satisfactory dosage level is achieved for combination, or the other medication is completely withdrawn. When therapy with this product alone is the objective, the transition should not be completed in less than two weeks.

MYSOLINE 50 mg. Tablet can be used to practical advantage when small fractional adjustments (upward or downward) may be required, as in the following circumstances:

- for initiation of combination therapy
- during "transfer" therapy
- for added protection in periods of stress or stressful situations that are likely to precipitate seizures (menstruation, allergic episodes, holidays, etc.)

HOW SUPPLIED: MYSOLINE *Tablets*—No. 430—Each tablet contains 250 mg. of primidone (scored), in bottles of 100 and 1,000. Also in unit dose package of 100. No. 431—Each tablet contains 50 mg. of primidone (scored), in bottles of 100 and 500. MYSOLINE *Suspension*—No. 3850—Each 5 cc. (teaspoonful) contains 250 mg. of primidone, in bottles of 8 fluidounces.

References: 1. Livingston, S.: Comprehensive Management of Epilepsy in Infancy, Childhood and Adolescence, Springfield, Ill., Charles C Thomas, 1972, pp. 6, 7, 584. 2. Grossman, H.J.: Ill. Med. J. *135*:260 (Mar.) 1969. 3. Scholl, M.L., in Conn, H.F.: Current Therapy 1973, Philadelphia, Saunders, 1973, pp. 675-7. 4. Metrick, S.: C.M.D. *37*:49 (Jan.) 1970. 5. Forster, F.M.: Med. Clin. North Am. *47*:1579 (Nov.) 1970. 6. White, P.T.: Wis. Med. J. *68*:178 (Apr.) 1969. 7. Millichap, J.G.: Drug Ther. *1*:15 (Oct.) 1971.



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1 Progress in Psychobiology and Physiological Psychology
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2 Principles of Neurobiological Signal Analysis

by EDMUND M. GLASER and DANIEL S. RUCHKIN

In recent years neurobiologists have increasingly come to analyze neuroelectric activity by techniques whose origin is in communication theory. This book is directed at researchers using these techniques by providing a broad survey of methods for computer analysis of neuroelectric signals recorded from microelectrodes and macroelectrodes. The methods discussed here have found wide application in neurobiological research and in clinical neurology.

The presentation begins with a discussion of the fundamental properties of signals, especially those generated within the nervous system. Spectra and covariance functions are introduced and their interrelationship described. Since neural signals are inherently noisy, there is a discussion of the probabilistic concepts associated with noise and how noise affects the detection and analysis of a signal. Following this introductory material, methods of signal processing such as sampling and analog-to-digital conversion are covered. The emphasis is upon computer methods of signal analysis and is intended to show the relationship between the signals generated by the nervous system and their sampled, quantized versions that are analyzed by a digital computer. The remainder of the book is devoted to a more detailed presentation of methods for studying the continuous and discrete electrical activity of the nervous system.

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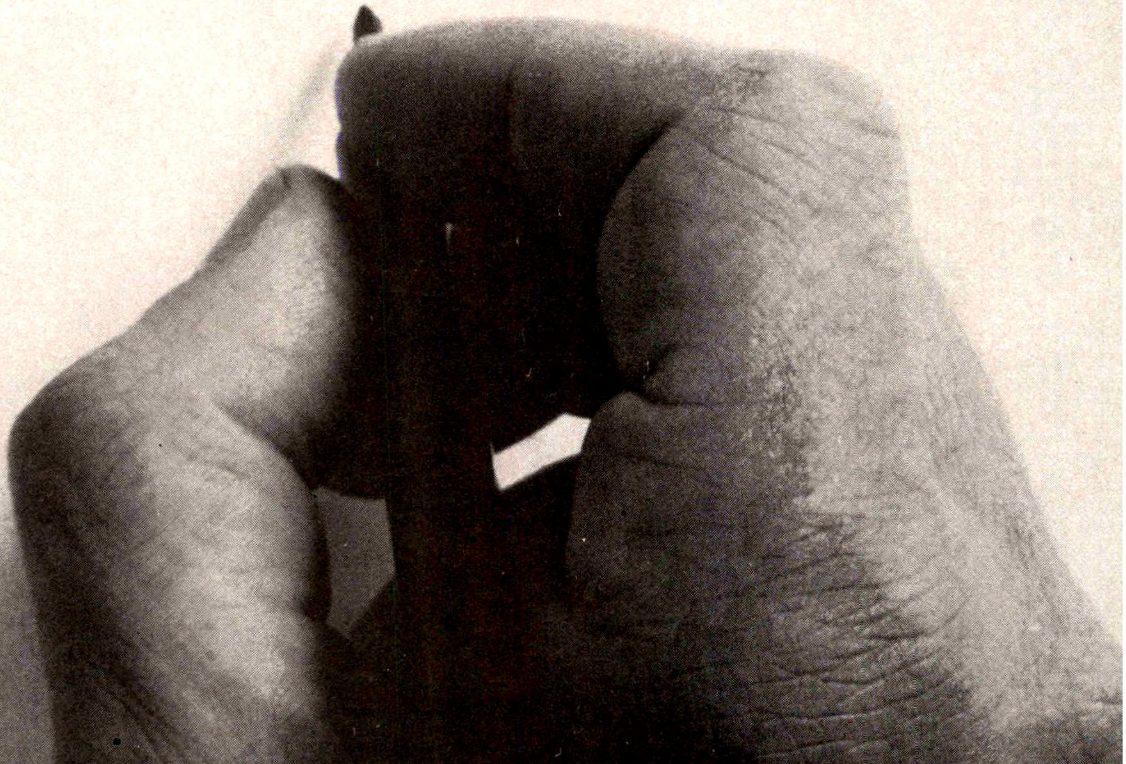
When
drug-induced
extrapyramidal
symptoms
complicate therapy



TABLETS: 0.5 mg, 1 mg, 2 mg INJECTION: 1.0 mg/ml

COGENTIN®

(BENZTROPINE MESYLATE | MSD)

highly effective against phenothiazine-induced extrapyramidal symptoms

(except tardive dyskinesia)

often permits needed chemotherapy to continue by controlling drug-induced extrapyramidal manifestations such as: *tremor, akathisia, motor restlessness, muscular rigidity, drooling, dystonic reactions.*

In some patients, however, the phenothiazine dosage may have to be reduced or discontinued. After one or two weeks, COGENTIN should be withdrawn to determine the continued need for it.

When given concomitantly with phenothiazines or other drugs with anticholinergic activity, patients should be advised to report gastrointestinal complaints promptly; paralytic ileus, sometimes fatal, has occurred in patients taking anticholinergic-type antiparkinsonism drugs, including COGENTIN, in combination with phenothiazines and/or tricyclic antidepressants.

Contraindications: Children under three years of age; use cautiously in older children.

Warnings: Safe use in pregnancy not established. May impair mental and/or physical abilities required for performance of hazardous tasks, such as operating machinery or driving a motor vehicle. When given concomitantly with phenothiazines or other drugs with anticholinergic activity, patients should be advised to report gastrointestinal complaints promptly; paralytic ileus, sometimes fatal, has occurred in patients taking anticholinergic-type antiparkinsonism drugs, including COGENTIN, in combination with phenothiazines and/or tricyclic antidepressants.

Precautions: Because of cumulative action, continued supervision is advisable. Closely observe patients with tendencies to tachycardia and those with prostatic hypertrophy. Dysuria may occur, but rarely becomes a problem. Large doses may cause complaints of weakness and inability to move particular muscle groups, requiring dosage adjustment.

Mental confusion and excitement may occur with large doses, or in susceptible patients; visual hallucinations reported occasionally. May intensify mental symptoms when used to treat extrapyramidal disorders due to neuroleptic drugs (e.g., phenothiazines) in patients with mental disorders; in such patients, increased doses of antiparkinsonian drugs can precipitate toxic psychosis; observe patients carefully, especially at the beginning of treatment or if dosage is increased. Tardive dyskinesia may appear in some patients on long-term therapy with phenothiazines and related agents, or may occur after therapy with these drugs has been discontinued; antiparkinsonism agents do not alleviate symptoms of tardive dyskinesia, and in some instances may aggravate them. COGENTIN is not recommended in tardive dyskinesia.

May produce anhidrosis; give with caution during hot weather, especially to the old, the chronically ill, the alcoholic, those who have central nervous system disease, those who do manual labor in a hot environment, and those with disturbances in sweating. If anhidrosis appears, reduce dosage so that ability to maintain body heat equilibrium is not impaired. Occurrence of glaucoma is a possibility; probably should not be used in angle-closure glaucoma.

Adverse Reactions: Adverse reactions may be anticholinergic or antihistaminic. Dry mouth, blurred vision, nausea, nervousness may develop. If dry mouth causes difficulty in swallowing or speaking, or loss of appetite and weight, reduce dosage, or discontinue drug temporarily. Vomiting occurs infrequently and may be controlled by temporary discontinuation, followed by resumption at a lower dosage. Constipation, numbness of the fingers, listlessness, and depression may develop. Occasionally, an allergic reaction, e.g., skin rash, develops; sometimes this can be controlled by reducing dosage, but occasionally requires discontinuation.

Note: Large doses generally cannot be tolerated by older patients and thin patients. Patients with a poor mental outlook are usually poor candidates for therapy. Do not terminate other antiparkinsonism agents abruptly; reduce gradually. When benztropine mesylate is used with levodopa the usual dose of each may need to be reduced.

How Supplied: Tablets in three strengths: 0.5 mg and 1 mg benztropine mesylate in bottles of 100, 2 mg benztropine mesylate in bottles of 100 and 1000, and 1 mg and 2 mg in single-unit packages of 100; Injection, in 2-ml ampuls, containing per ml: 1.0 mg benztropine mesylate, 9.0 mg sodium chloride, and water for injection q.s.

For more detailed information, consult your MSD representative or see full prescribing information. Merck Sharp & Dohme, Division of Merck & Co., INC., West Point, Pa. 19486

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addendum

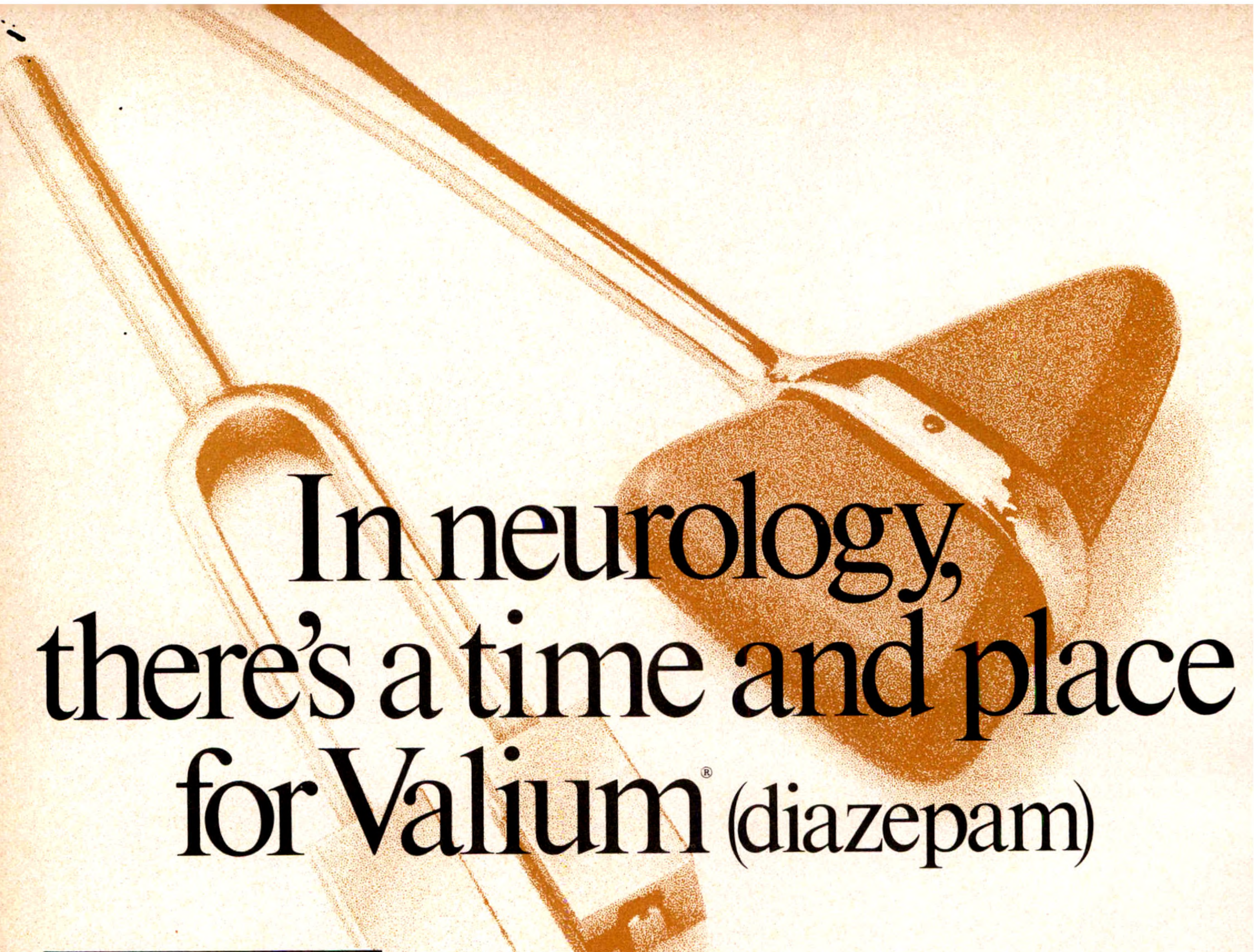
Facts about dosage schedules of COGENTIN (Benztropine Mesylate | MSD)

In treating extrapyramidal symptoms due to neuroleptic drugs, such as phenothiazines and butyrophenones, the recommended dosage of COGENTIN is 1 to 4 mg once or twice a day orally or parenterally. Dosage must be individualized according to the need of the patient. Some patients require more than recommended; others do not need as much. The tablet form should be used when patients are able to take oral medication.

When extrapyramidal symptoms develop soon after initiation of treatment with neuroleptic drugs, they are likely to be transient. One to 2 mg COGENTIN orally two or three times a day usually provides relief within one or two days. After one or two weeks, COGENTIN should be withdrawn to determine the continued need for it. If symptoms recur, COGENTIN can be reinstituted.

Certain extrapyramidal disorders that develop slowly may not respond to COGENTIN. COGENTIN is not recommended in tardive dyskinesia.

For more detailed information, see full prescribing information.



In neurology, there's a time and place for Valium® (diazepam)

For the neurologic patient, when psychic tension does not respond to reassurance alone, Oral Valium® can be beneficial

When significant psychic tension forms part of the clinical picture, it must be considered along with the neurological problem. In most instances, Valium can produce the desired psychotherapeutic effect, reducing tension and anxiety. The beneficial effect of Valium is usually pronounced and rapid. Improvement generally becomes evident within a few days, although some patients may require a longer period. Valium is contraindicated in acute narrow angle glaucoma but may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Valium is available in scored tablets of three strengths, so dosage can be easily individualized to gain optimal response. And, if anxiety and tension are especially troublesome at bedtime, an *h.s.* dose can be added to a *b.i.d.* or *t.i.d.* regimen.

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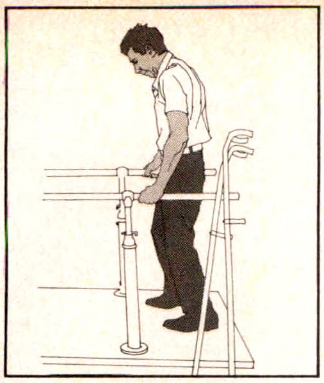
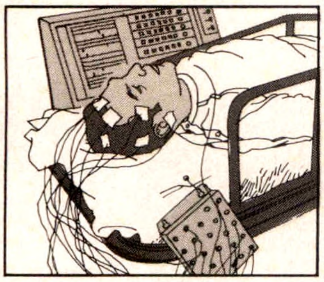


In paraplegia, cerebral palsy, athetosis, stiff-man syndrome and tetanus, adjunctive Valium (diazepam) can help reduce spasticity

Patients with upper motor neuron disorders that cause paraplegia and cerebral palsy can greatly benefit by the adjunctive use of Oral Valium — or Injectable Valium, where appropriate, in the usual dosage for muscle spasm. It has proved valuable in athetosis, too. Valium makes possible improved voluntary muscle performance, thereby encouraging patient cooperation and confidence during therapy and rehabilitation.

Injectable Valium has also been useful in stiff-man syndrome or in tetanus to reduce characteristic skeletal muscle spasm and resulting rigidity. Response is usually prompt and improvement sustained in the control of muscular rigidity and convulsive spasms. *For tetanus, only the parenteral form of Valium is indicated,* and larger doses may be needed with a repeat dose, if necessary, in 3 to 4 hours. Use of Injectable Valium in children under 12 and tablets in infants are contraindicated.



Adjunctive Injectable Valium (diazepam) widely cited in the literature* for its effectiveness in status epilepticus

The speed, efficacy and relative safety of Injectable Valium have made it one of the most important adjuncts available in the treatment of status epilepticus. It acts promptly to control this disorder as well as other severe recurrent convulsive seizures. (Before administering I.V., please consult Warnings and Dosage sections of Product Information on following page.)

Oral Valium can also be used adjunctively in various convulsive disorders. Often it will reduce the frequency and/or severity of the seizures, though it has not proven useful as sole therapy. As with other anticonvulsant agents, there is a possibility of increased frequency and/or severity of grand mal seizures which may require greater doses of standard anticonvulsant medication. Abrupt withdrawal of Valium may also temporarily cause a similar effect.

*__References:__ **1.** Brett EM: *Dev Med Child Neurol 12*:655-659, 1970. **2.** Carter S, Gold AP: *Pediatrics 44*:732-733, Nov 1969. **3.** Merritt HH: *Med Clin North Am 56*:1225-1231, Nov 1972. **4.** Nicol CF, Tutton JC, Smith BH: *Neurology 19*:332-343, Apr 1969. **5.** Sawyer GT, Webster DD, Schut LJ: *JAMA 203*:913-918, March 11, 1968. **6.** Swash M: *Br J Hosp Med 8*:269-272, Sept 1972. **7.** Greenblatt DJ, Shader RI: *Benzodiazepines in Clinical Practice.* New York, Raven Press, 1974, pp. 129-130.

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Contraindications: Use of Injectable in infants and Tablets in children under 6 months of age; known hypersensitivity to drug; acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: As with most CNS-acting drugs, caution patients against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Advise patients against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Keep addiction-prone individuals (drug addicts or alcoholics) under careful surveillance because of their predisposition to habituation and dependence. Use of any drug in pregnancy, nursing women or in women of childbearing potential requires that expected benefit be weighed against possible hazard.

ORAL: Not of value in treatment of psychotic patients; should not be employed in lieu of appropriate treatment. When using oral form adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increase in dosage of standard anticonvulsant medication; abrupt withdrawal in such cases may also be associated with temporary increase in frequency and/or severity of seizures.

INJECTABLE: *When used I.V., the following procedures should be undertaken to reduce the possibility of venous thrombosis, phlebitis, local irritation, swelling, and, rarely, vascular impairment. Inject slowly, taking at least one minute for each 5 mg (1 ml) given; do not use small veins,* i.e., *dorsum of hand or wrist; extreme care should be taken to avoid intra-arterial administration or extravasation. Do not mix or dilute with other solutions or drugs; do not add to I.V. fluids.*

Administer with extreme care to elderly or very ill and those with limited pulmonary reserve because of possibility of apnea and/or cardiac arrest; resuscitative facilities should be available. When used with narcotic analgesic, eliminate or reduce narcotic dosage at least ⅓ and administer in small increments. Not recommended for OB use until additional information is available. Should not be administered to patients in shock, coma or in acute alcoholic intoxication with depression of vital signs.

Precautions: If combined with other psychotropics or anticonvulsants, carefully consider individual pharmacologic effects—particularly with known compounds which may potentiate action of Valium (diazepam), such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants. Protective measures indicated in highly anxious patients with accompanying depression who may have suicidal tendencies. Observe usual precautions in impaired hepatic function; avoid accumulation in patients with compromised kidney function. Limit oral dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation (initially 2 to 2½ mg once or twice daily, increasing gradually as needed or tolerated).

INJECTABLE: Laryngospasm and increased cough reflex are possible during peroral endoscopic procedures; use topical anesthetic and have necessary countermeasures available; hypotension or muscular weakness possible, particularly when used with narcotics, barbiturates or alcohol. Use lower doses (2 to 5 mg) for elderly and debilitated; safety and efficacy in children under 12 not established.

Adverse Reactions: Side effects most commonly reported were drowsiness, fatigue and ataxia. Infrequently encountered were confusion, constipation, depression, diplopia, dysarthria, headache, hypotension, incontinence, jaundice, changes in libido, nausea, changes in salivation, skin rash, slurred speech, tremor, urinary retention, vertigo and blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances and stimulation have been reported; should these occur, use of the drug should be discontinued. Because of isolated reports of neutropenia and jaundice, periodic blood counts and liver function tests are advisable during long-term therapy. Minor changes in EEG patterns, usually low-voltage fast activity, have been observed in patients during and after Valium therapy and are of no known significance.

INJECTABLE: Venous thrombosis and phlebitis at injection site, hypoactivity, syncope, bradycardia, cardiovascular collapse, nystagmus, urticaria, hiccups, neutropenia.

In peroral endoscopic procedures, coughing, depressed respiration, dyspnea, hyperventilation, laryngospasm and pain in throat or chest have been reported.

Dosage: Individualized for maximum beneficial effect.

ORAL—*Adults:* Tension, anxiety and psychoneurotic states, 2 to 10 mg *b.i.d.* to *q.i.d.*; acute alcohol withdrawal, 10 mg *t.i.d.* or *q.i.d.* in first 24 hours, then 5 mg *t.i.d.* or *q.i.d.* as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg *t.i.d.* or *q.i.d.*; adjunctively in convulsive disorders, 2 to 10 mg *b.i.d.* to *q.i.d. Geriatric or debilitated patients:* 2 to 2½ mg 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) *Children:* 1 to 2½ mg *t.i.d.* or *q.i.d.* initially, increasing as needed and tolerated (not for use under 6 months).

INJECTABLE: Usual initial adult dose is 2 to 20 mg I.M. or I.V., depending on indication and severity. Larger doses may be required in some conditions (tetanus). In acute conditions injection may be repeated within 1 hour, although interval of 3 to 4 hours is usually satisfactory. Lower doses (usually 2 to 5 mg) with slow dosage increase for elderly or debilitated patients and when sedative drugs are added. (See Warnings and Adverse Reactions.)

I.M. use: by deep injection into the muscle.

I.V. use: inject slowly, take at least one minute for each 5 mg (1 ml) given. Do not use small veins, i.e., *dorsum of hand or wrist. Use extreme care to avoid intra-arterial administration or extravasation. Do not mix or dilute with other solutions or drugs; do not add to I.V. fluids.*

Moderate psychoneurotic reactions, 2 to 5 mg I.M. or I.V. and severe psychoneurotic reactions, 5 to 10 mg I.M. or I.V., repeat in 3 to 4 hours if necessary; acute alcoholic withdrawal, 10 mg I.M. or I.V. initially, then 5 to 10 mg in 3 to 4 hours if necessary; muscle spasm, 5 to 10 mg I.M. or I.V. initially, then 5 to 10 mg in 3 to 4 hours if necessary (tetanus may require larger doses); status epilepticus, severe recurrent convulsive seizures, 5 to 10 mg I.M. or I.V. initially, repeat in 2 to 4 hours if necessary. In endoscopic procedures, titrate I.V. dosage to desired sedative response, generally 10 mg or less but up to 20 mg (if narcotics are omitted) immediately prior to procedure; if I.V. cannot be used, 5 to 10 mg I.M. approximately 30 minutes prior to procedure. As preoperative medication, 10 mg I.M.; in cardioversion, 5 to 15 mg I.V., within 5 to 10 minutes prior to procedure. Once acute symptomatology has been properly controlled with injectable form, patient may be placed on oral form if further treatment is required.

Management of Overdosage: Manifestations include somnolence, confusion, coma and diminished reflexes. Monitor respiration, pulse, blood pressure; employ general supportive measures, I.V. fluids, adequate airway. Immediate gastric lavage indicated for overdosage with tablets. Use levarterenol or metaraminol for hypotension, caffeine and sodium benzoate for CNS-depressive effects. Dialysis is of limited value.

Supplied: Tablets, 2 mg, 5 mg and 10 mg—bottles of 100 and 500; Tel-E-Dose® packages of 100, available in trays of 4 reverse-numbered boxes of 25, and in boxes containing 10 strips of 10; Prescription Paks of 50, available singly and in trays of 10. Ampuls, 2 ml, boxes of 10; Vials, 10 ml, boxes of 1; Tel-E-Ject® (disposable syringes), 2 ml, boxes of 10. Each ml contains 5 mg diazepam, compounded with 40% propylene glycol, 10% ethyl alcohol, 5% sodium benzoate and benzoic acid as buffers, and 1.5% benzyl alcohol as preservative.

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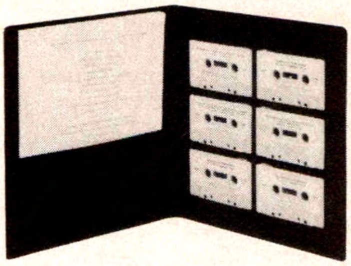
NEW APPROACHES TO HEADACHE MANAGEMENT

edited by
Seymour Diamond, M.D.
Director of the Diamond Headache Clinic, Ltd., Chicago



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CEREBRAL DURAL SINUSES AND THEIR TRIBUTARIES *by* **Jefferson Browder,** *Veterans Administration Hospital, East Orange, New Jersey, and* **Harry A. Kaplan,** *New Jersey Medical School, Newark.* The accumulated information derived from all sources is related in a clear and concise style in this book. Specimens utilized for this study were from all age groups, midfetal through old age. Vinylite casts of selected parts of the sinuses and their tributaries were made in approximately one-half of the specimens. Patterns of both the major sinuses and joining tributaries were classified when feasible. Due to the broad surgical experience of the authors, this book has a distinct clinical flavor which will furnish neuroradiologists and neurosurgeons with an additional point of view without interfering with the fundamentally anatomical perspective of the book. *'76, 140 pp., 66 il., $14.75*

BRAIN TUMOR CHEMOTHERAPY *by* **Derek Fewer,** *Univ. of Manitoba, Winnipeg, Manitoba, Canada;* **Charles B. Wilson** *and* **Victor A. Levin,** *both of the Univ. of California, San Francisco. Foreword by* **Edwin B. Boldrey.** *(3 Contributors)* The authors of this book define the concepts for a strategic approach to the use of oncolytic agents. They review their clinical experiences and provide a background for the selection of drugs and drug schedules as newer single agents, drug combinations and multimodality approaches applied to brain tumors. This book is directed toward anyone—oncologist, neurologist, or neurosurgeon—who wants to understand and approach the chemotherapy of brain tumors. *'76, 224 pp., 11 il., 4 tables, $17.50*

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a combination of carbidopa and levodopa

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See last page of advertisement for brief summary of prescribing information.

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Symptomatic relief

SINEMET usually relieves the major symptoms of Parkinson's disease:

- **rigidity**
- **bradykinesia**
- **tremor**

Improved performance of daily activities

Symptomatic relief of Parkinson's disease may enable some patients to carry out such routine daily activities as:

- **walking**
- **dressing**
- **eating**
- **maintaining personal hygiene**

SINEMET is contraindicated in:

- Patients receiving monoamine oxidase inhibitors. These inhibitors must be discontinued at least two weeks prior to initiating therapy with SINEMET.
- Patients with known hypersensitivity to this drug.
- Patients with narrow-angle glaucoma. (Patients with chronic wide-angle glaucoma may be treated cautiously if intraocular pressure is well controlled and the patient is monitored carefully for changes in intraocular pressure during therapy.)
- Patients with suspicious, undiagnosed skin lesions or a history of melanoma. Because levodopa may activate a malignant melanoma, SINEMET should not be used in these patients.

All cautionary information with levodopa also applies to SINEMET. Turn to the back page for additional information.

and that difference often depends on proper dosage

Start with SINEMET-25/250 for patients transferred from levodopa

SINEMET-25/250 t.i.d. or q.i.d. is the suggested starting dosage for most patients. And, since most patients can be maintained on only one or two tablets t.i.d., SINEMET-25/250 is the most convenient strength.

Enough carbidopa

A daily dosage of SINEMET should be chosen that will provide approximately 70 to 100 mg of carbidopa because studies show that peripheral dopa decarboxylase is saturated by carbidopa at approximately 70 to 100 mg per day.

SINEMET-25/250 is the most convenient strength for providing the proper amount of carbidopa necessary for optimal therapeutic response. For example, one SINEMET-25/250 t.i.d. provides 75 mg of carbidopa—an adequate amount of carbidopa for maximum utilization of levodopa with less nausea and vomiting.

Enough levodopa

A daily dosage of SINEMET should be chosen that will provide approximately 25 percent of the previous levodopa daily dosage.

SINEMET-25/250 is the most convenient strength for providing the proper amount of levodopa. For example, one SINEMET-25/250 t.i.d. provides 750 mg of levodopa—the proper amount of levodopa for patients previously on 3000 mg of levodopa. (Please refer to the addendum for dosage guidelines for patients who are not on levodopa or who have been taking less than 1500 mg per day.)

Other dosage considerations

Discontinue levodopa at least 8 hours before SINEMET is begun. A time interval shorter than 8 hours may increase the risk of levodopa-induced adverse reactions.

Because of increased brain dopamine levels, both therapeutic and adverse reactions (specifically, involuntary movements and mental disturbances), occur at lower doses and more rapidly with SINEMET than with levodopa. In order to reduce adverse reactions, it is necessary to individualize therapy and to monitor the patient closely during the dose adjustment period. The occurrence of involuntary movements may require dosage reduction. Blepharospasm may be a useful sign of excess dosage in some patients.

Instruct patients not to take levodopa with SINEMET unless you specifically recommend it.

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See following page for brief summary of prescribing information.

Dosage Guideline

Addendum

SINEMET-25/250

containing 25 mg carbidopa and 250 mg levodopa

For most patients transferred from levodopa

Discontinuing levodopa: Since levodopa should be discontinued at least 8 hours before starting SINEMET, start SINEMET the morning after the last nighttime dose of levodopa.

Selecting a starting dose: The starting dose for SINEMET should provide about 25 percent of previous levodopa requirements.

Usual starting dose: SINEMET-25/250 t.i.d. or q.i.d.

Adjusting dose: Add or delete ½ or 1 tablet SINEMET-25/250 as needed at 1-day intervals.

Usual maintenance dose: 3 to 6 tablets of SINEMET-25/250 given in divided doses.

Maximum dose: 8 tablets of SINEMET-25/250 daily. Alternatively, dosage may be titrated to 6 tablets of SINEMET-25/250 a day, and further adjusted with increments of levodopa.

Also available SINEMET-10/100
containing 10 mg carbidopa and 100 mg levodopa

For patients who are not on levodopa or for patients on levodopa who have been taking less than 1500 mg per day:
Start with SINEMET-10/100 t.i.d. and increase by 1 tablet every day or every other day until a dosage of 6 tablets is reached. If further titration is necessary, *change* the patient to SINEMET-25/250, at a dosage of 1 tablet t.i.d.
NOTE: Most patients on SINEMET will eventually require SINEMET-25/250 for optimal control of the symptoms of Parkinson's disease.

For full details of dosage and administration see prescribing information.

Sinemet®

a combination of carbidopa and levodopa

can mean a world of difference for some parkinsonian patients

When SINEMET is to be given to patients who are being treated with levodopa, levodopa must be discontinued at least 8 hours before therapy with SINEMET is started. In order to reduce adverse reactions, it is necessary to individualize therapy. See the Warnings (below) and Dosage and Administration sections in the full prescribing information before initiating therapy.

Contraindications: MAO inhibitors and SINEMET should not be given concomitantly. MAO inhibitors must be discontinued at least 2 weeks prior to initiating therapy with SINEMET.

SINEMET is contraindicated in patients with known hypersensitivity to this drug and in narrow-angle glaucoma.

Because levodopa may activate a malignant melanoma, it should not be used in patients with suspicious, undiagnosed skin lesions or history of melanoma.

Warnings: Levodopa must be discontinued at least 8 hours before SINEMET is started. SINEMET should be substituted at a dosage that will provide approximately 25 percent of the previous levodopa dosage. (See Dosage and Administration section of full prescribing information.) Patients taking SINEMET should be instructed not to take additional levodopa unless prescribed.

As with levodopa, SINEMET may cause involuntary movements and mental disturbances. These reactions may be due to increased brain dopamine following administration of levodopa. All patients should be observed carefully for development of depression with concomitant suicidal tendencies. Treat with caution patients with past or current psychoses. *Because carbidopa permits more levodopa to reach the brain and, thus, more dopamine to be formed, dyskinesias may occur at lower dosages and sooner with SINEMET than with levodopa.* Occurrence of dyskinesias may require dosage reduction.

SINEMET should be administered cautiously to patients with severe cardiovascular or pulmonary disease, bronchial asthma, renal, hepatic or endocrine disease.

Exercise care in administering SINEMET, as with levodopa, to patients with history of myocardial infarction who have residual atrial, nodal, or ventricular arrhythmias. In such patients, cardiac function should be monitored with particular care during period of initial dosage adjustment, in a facility with provisions for intensive cardiac care.

As with levodopa, there is possibility of upper G.I. hemorrhage in patients with history of peptic ulcer.

Usage in Pregnancy and Lactation: Although effects of SINEMET on human pregnancy and lactation are unknown, both levodopa and combinations of carbidopa and levodopa have caused visceral and skeletal malformations in rabbits. Use of SINEMET in women of childbearing potential requires that anticipated benefits of the drug be weighed against possible hazards to mother and child. SINEMET should not be given to nursing mothers.

Usage in Children: Safety of SINEMET in patients under 18 has not been established.

Precautions: As with levodopa, periodic evaluations of hepatic, hematopoietic, cardiovascular, and renal function are recommended during extended therapy.

Patients with chronic wide-angle glaucoma may be treated cautiously with SINEMET provided intraocular pressure is well controlled and patient is monitored carefully for changes in intraocular pressure during therapy.

Symptomatic postural hypotension can occur. For this reason, SINEMET should be given cautiously to patients on antihypertensive drugs. When SINEMET is started, dosage adjustment of the antihypertensive drug may be required. (For patients receiving pargyline, see the contraindication on MAO inhibitors.)

Since phenothiazines and butyrophenones may reduce therapeutic effects of levodopa, they should be administered with caution if concomitant administration with SINEMET is necessary, and patients should be carefully observed for loss of antiparkinsonian effect.

Adverse Reactions: Most common serious adverse reactions occurring with SINEMET are choreiform, dystonic, and other involuntary movements. Other serious adverse reactions are mental changes including paranoid ideation and psychotic episodes, depression with or without development of suicidal tendencies, and dementia. Convulsions also have occurred; however, a causal relationship with SINEMET has not been established.

A common but less serious effect is nausea.

Less frequent adverse reactions are cardiac irregularities and/or palpitations, orthostatic hypotensive episodes, bradykinetic episodes (the "on-off" phenomenon), anorexia, vomiting, and dizziness.

Rarely, G.I. bleeding, development of duodenal ulcer, hypertension, phlebitis, hemolytic anemia, leukopenia, and agranulocytosis have occurred.

Other adverse reactions reported with levodopa include dry mouth, dysphagia, sialorrhea, abdominal pain and distress, ataxia, increased hand tremor, headache, numbness, weakness and faintness, bruxism, confusion, insomnia and nightmares, hallucinations and delusions, agitation and anxiety, malaise, fatigue, euphoria, muscle twitching and blepharospasm (may be taken as an early sign of excess dosage; consider dosage reduction at this time), trismus, burning sensation of tongue, bitter taste, diarrhea, constipation, flatulence, flushing, skin rash, increased sweating, bizarre breathing patterns, urinary retention, urinary incontinence, diplopia, blurred vision, dilated pupils, hot flashes, weight gain or loss, dark sweat and/or urine, oculogyric crises, sense of stimulation, hiccups, edema, loss of hair, hoarseness, priapism, and activation of latent Horner's syndrome.

Abnormalities in laboratory tests may include elevations of blood urea nitrogen, SGOT, SGPT, lactic dehydrogenase, bilirubin, alkaline phosphatase, protein-bound iodine, and positive Coombs test. More commonly, levels of blood urea nitrogen, creatinine, and uric acid are lower during administration of SINEMET than with levodopa.

Overdosage: Management of acute overdosage with SINEMET is basically the same as management of acute overdosage with levodopa; however, pyridoxine is not effective in reversing the actions of SINEMET.

How Supplied: Tablets SINEMET-10/100 and Tablets SINEMET-25/250 are supplied in bottles of 100.

For more detailed information, consult your MSD representative or see full prescribing information. Merck Sharp & Dohme, Division of Merck & Co., INC., West Point, Pa. 19486

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Original Contributions

Acromutilating, Paralyzing Neuropathy With Corneal Ulceration in Navajo Children

Otto Appenzeller, MD, PhD; Mario Kornfeld, MD; Russell Snyder, MD

• Four Navajo children had a mutilating neuropathy with severe motor involvement. The disorder appears to be recessively inherited and is present from the earliest observable age. Manifestations include severe anesthesia, corneal ulceration, painless fractures, acral mutilation, and weakness. Mental function is normal. Sural nerves are practically devoid of myelinated fibers that show no evidence of regeneration. Unmyelinated axons show degenerative and regenerative morphologic and histometric features. Onion bulb formation is absent. We believe this neuropathy is a distinct clinical entity.

(*Arch Neurol* 33:733-738, 1976)

Sural nerve biopsies have contributed to the study of peripheral neuropathies. In patients with peripheral nerve disease, morphologic evidence of destruction and regeneration of both myelinated and unmyelinated fibers is usually found. Selective loss of fiber types occurs in some disorders. In amyloid neuropathy, acute pandysautonomia,[1] and familial dysautonomia,[2] unmyelinated fibers are affected predominantly. We now report a condition in which there is an almost total loss of myelinated fibers, with relative sparing of unmyelinated axons. The patients were Navajo Indians with severe acral mutilation, corneal ulceration, and marked weakness.

REPORT OF CASES

Case 1.—An 8-year-old boy was examined in March 1970. Birth weight was unknown. Though intellectually normal, he had never been able to walk. He had two brothers and four sisters; all were normal.

Clinical and Laboratory Findings

	Case 1	Case 2	Case 3	Case 4
Age, yr, at examination	8	6	6	2
Neuromuscular disease in family	+	−	+	+
Delay in walking	+	+	+	+
Progressive symptoms	−	−	−	−
Normal intelligence	+	+	+	+
Corneal ulceration	+	+	+	+
Cutaneous ulceration and decreased sensation (all modalities)	+	+	+	+
Muscle weakness, atrophy, and hypotonia	+	+	+	+
Painless fractures	−	−	+	−
Deep tendon jerks	−	−	−	−
Cerebrospinal fluid protein, mg/100 ml	16	73	. . .	90
Creatinine phosphokinase, sigma units (normal, 0-12)	9	5	. . .	9.5
Ulnar nerve conduction velocities, meter/sec	28.4	. . .	36	. . .
Electromyographic evidence of denervation	+	+	−	−
Muscle biopsy evidence of denervation	−	+	−	+

Accepted for publication Feb 2, 1976.
From the departments of neurology (Drs Appenzeller and Snyder) and pathology (Dr Kornfeld), University of New Mexico School of Medicine, Albuquerque.
Reprint requests to Department of Neurology, University of New Mexico School of Medicine, Albuquerque, NM 87131 (Dr Appenzeller).

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A paternal first cousin had "stiff legs," was unable to walk, and died at age 5 years. A paternal second cousin suffered from "cerebral palsy" and died at 5 years of age.

The patient could converse in Navajo. Speech and intelligence were normal. Findings from general examination were normal, except for depigmented skin lesions on the legs and bilateral central corneal opacities. Cranial nerve functions were normal. All extremities were hypotonic, with decreased muscle mass in the legs. Weakness was marked in all limbs, though he could resist gravity. No fasciculations were seen. Tendon reflexes were barely obtainable in the arms and absent in the legs. Abdominal reflexes were absent. There was no tremor. No response was obtained to superficial or deep painful stimulation of limbs. Position and vibration sense could not be evaluated. Responsiveness to painful stimulation on the paraspinous areas and face was reduced. Nerves were not palpable. Results of laboratory and other investigations are given in the Table.

Case 2.—A 6-year-old Navajo girl was examined in March 1966. Birth was normal. She first walked at age 18 months, but gait was never normal. She had two normal and one mentally retarded siblings. She was of normal intelligence. Findings from general physical examination were normal. Eye movements and fundi were normal. Corneal ulceration was present. Neurologic examination showed normal cranial nerve function; all extremities were hypotonic. Weakness and atrophy were more marked distally. Tendon and superficial reflexes were absent. No tremor could be found. Gait was widebased without ataxia. Fasciculations were not seen. No response to painful stimulation could be obtained over the entire body. Position and vibration sense could not be evaluated. Results of laboratory and other investigations are given in the Table.

Case 3.—This Navajo child sat at 5 months, but did not walk until age 2 years. He was the brother of Patient 4. Three other siblings and the parents were normal. At age 6, he was alert and could speak Navajo and Spanish. Intelligence was normal. Findings from general examination were normal, except for elevated crusted lesions 1 to 3 cm in diameter on bony prominences of all limbs. The right tibia was bowed anteriorly and the right ankle everted. Bilateral corneal opacities were present. Neurologic examination showed impaired corneal reflexes, decreased muscle mass in the legs, generalized hypotonia, and slight tremor on finger-to-nose testing. Tendon reflexes were absent, except for depressed biceps jerks. Superficial reflexes were absent. Notably decreased responses to touch, vibration, joint position, and painful stimulation were found all over the body. Roentgenographic examinations of the skull, spine, and chest were normal, but there was a deformity of the middle third of the left tibia and fibula, resulting from previous painless fractures. Results of laboratory and other investigations are given in the Table.

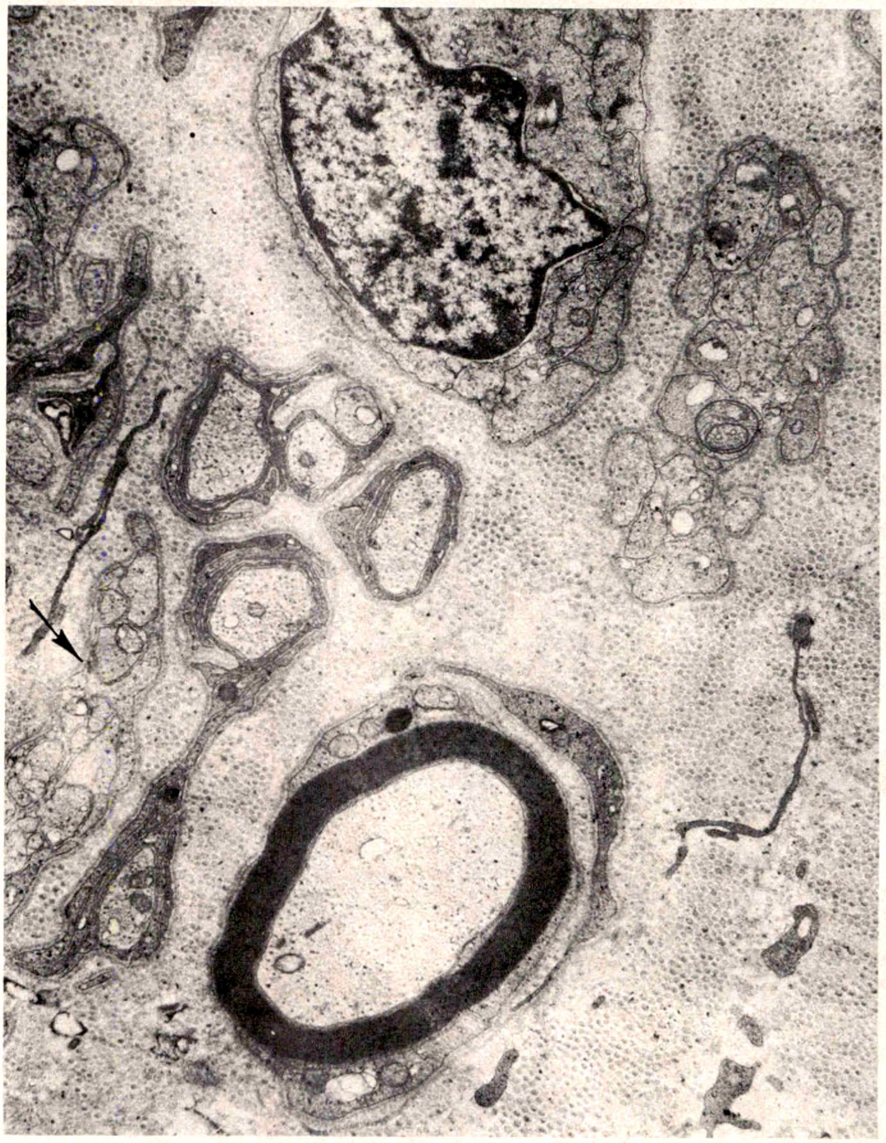

Fig 1.—Photomicrograph (case 1) showing one small myelinated fiber partially surrounded by crescent-shaped Schwann cell process. Note two irregular denervated Schwann cell bands (right upper corner) and one containing several axons (arrow) (original magnification ×22,500).

Case 4.—This girl, sister of patient 3, was only able to sit at age 2 years. She appeared of normal intelligence, and findings from general examination were normal. Bilateral corneal opacities were present. Results of neurologic examination were normal, except for severe hypotonia and wasting of all limbs. Tendon reflexes were absent, and some withdrawal from painful stimulation could be obtained. An electroencephalogram was normal. Results of laboratory and other investigations are given in the Table. The child died at home seven months after examination; an autopsy was not performed.

METHODS

Biopsy specimens were obtained from sural nerves at the ankle. The tissue was fixed in a 3.7% buffered formaldehyde

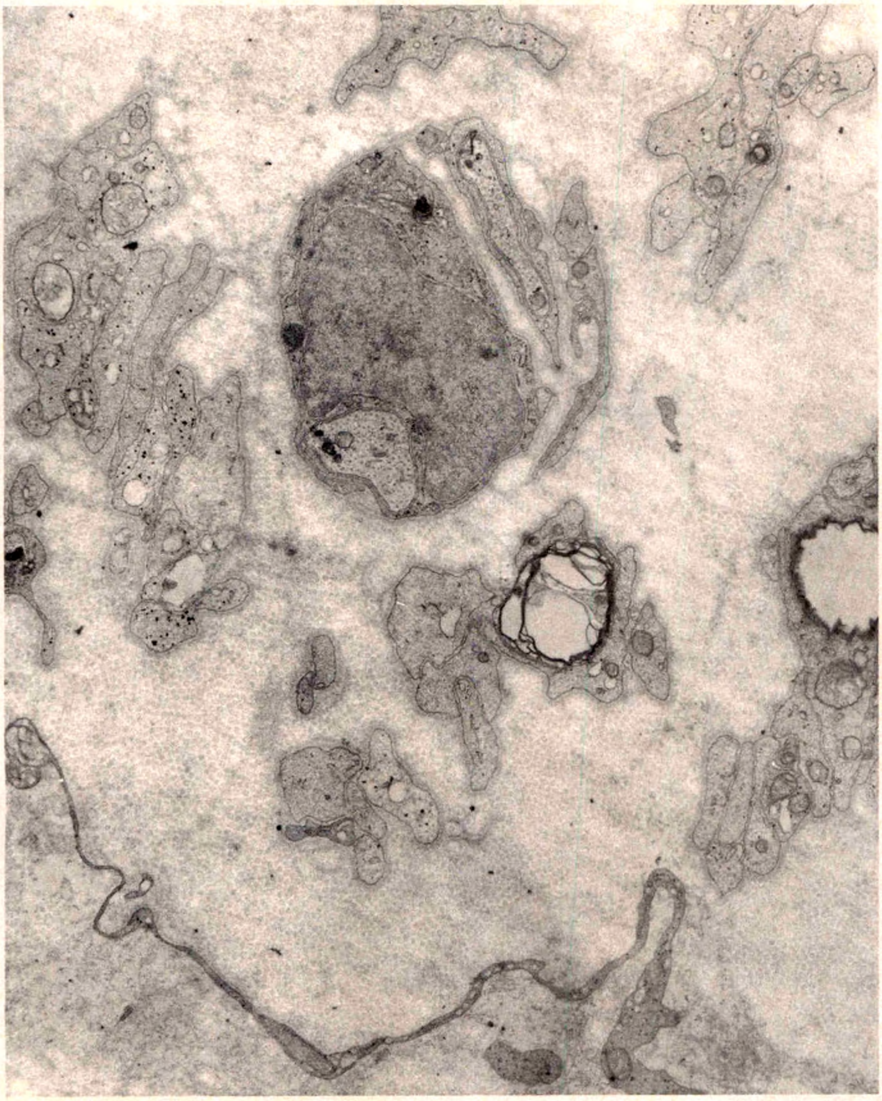

Fig 2.—Photomicrograph (case 1) showing several denervated Schwann cell bands; two contain myelin remnants. Note many interdigitating various-shaped Schwann cell processes (center) and unmyelinated axon (top center) surrounded by two flattened Schwann cell processes (original magnification ×40,000).

solution and stained with hematoxylin-eosin, Masson trichrome, and Bodian stains. One portion of the nerve was fixed in 1% osmium tetroxide and examined unstained.

Tissue for electron microscopy was immersed, immediately after removal, in cold 2.5% sodium cacodylate buffered glutaraldehyde, postfixed in 1% osmium tetroxide dehydrated, and embedded in epoxy resin. After sectioning with glass or diamond knives on an ultramicrotome, the sections were stained with uranyl acetate and lead citrate and examined in an electron microscope.

One part of the sural nerve was immediately frozen and, after cleaning, subjected to gas-liquid chromatography. A dual-column, temperature-programmed gas chromatograph with strontium chloride Sr 90 ionization detectors and 1.83-meter stainless steel columns packed with 4% SE-30 on a solid support chromatography medium, 80 to 100 mesh, was used.

The method for the preparation of tissues is fully described elsewhere.[3] Briefly, an aliquot of 100 ml of wet blotted tissue was heated with tetramethylammonium hydroxide reagent, which dissolved it. The digested tissue was evaporated to dryness, cooled, and then extracted with 0.5 ml of ethanol. A quantitative estimate of the composition of the nerve was gained by summating the area of the nine most prominent peaks of the chromatograms, and the percentage area occupied by each peak was then calculated. A tentative identification of the chromatogram peaks is as follows: B, myristic; D, palmitic; E, oleic; F, stearic; I, cholesterol; peaks A,C,G, and H have not been identified. The gas-liquid chromatograms and quantitative data of four patients were compared to those obtained from five control nerves from children of similar age.

RESULTS

The clinical findings and results of special investigations are given in the Table.

Morphologic Findings

All sural nerve biopsy specimens consisted of 6 to 12 fascicles of nerve fibers and showed similar abnormalities. There was total absence of neurokeratin network in sections stained with hematoxylin-eosin. A slight increase in the number of Schwann cell nuclei was seen in the youngest patient (case 4). A moderate increase in thickness of the perineurium was seen in some sections (cases 1 and 2). No myelinated fibers were found in osmium-treated cross sections, but in longitudinal sections an occasional myelinated fiber segment could be seen. No osmiophilic breakdown products of myelin were present. An average number of axons was evident on silver stains in case 4, but the number of axons was decreased in cases 1 and 2.

Ultrastructure

The ultrastructural features were similar in all nerves. A 1μ-thick section embedded in epoxy resin showed an extraordinary paucity of myelinated fibers. Several fascicles without a single myelinated fiber were present; other fascicles contained only two to eight myelinated fibers. Numerous thin sections had to be screened in order to find one myelinated fiber. These fibers showed some ultrastructural abnormalities. The largest myelinated axons measured 1.7μ in diameter. Reduplication of basement membranes, at least along a portion of the fiber circumference, was found on all myelinated fibers. These reduplicated basement membranes were intricately folded. The Schwann cell cytoplasm of some fibers contained π granules in larger than usual numbers for the age of the patients. Some fibers were surrounded by crescent-shaped Schwann cell processes. Their basement membranes were usually continuous, with reduplicated basement membranes surrounding myelinated fibers (Fig 1). Only two myelinated fibers were found in thick sections of four fascicles in another nerve (case 1). The larger axon measured 1.2μ and the smaller 1.0μ in diameter. These axons, their myelin sheaths, and Schwann cell cytoplasm showed no ultrastructural abnormalities, but duplication and folding of the basement membrane were present.

Nonmyelinated axons were surrounded by multiple, attenuated long processes of Schwann cells that extended far into the surrounding endoneurium, giving the structures a bizarre shape. The electron density of the Schwann cell cytoplasm varied considerably from process to process. Occasional attenuated Schwann cell processes were wrapped two or three times around a nonmyelinated axon. Normal Schwann cells were sometimes opposed by several crescent-shaped, attenuated Schwann cell processes that contained unmyelinated axons or were denervated. Such structures were usually connected by continuous, often duplicated and folded, basement membranes. Very small diameter, unmyelinated axons were found in large bands of Schwann cells. Other large Schwann cell bands of irregular or oval shape, often measuring up to 6.8μ, in longitudinal axis were devoid of axons, but contained occasional degenerating portions of myelin sheath (Fig 2). Rounded, denervated Schwann cell bands were also seen. An abnormal increase in endoneurial collagen and fibroblasts was evident. Some Schwann cell bands were composed of various-shaped interdigitating processes (Fig 2). Most unmyelinated axons were normal ultrastructurally, but a number had an increase of mitochondria and dense bodies. The filaments were densely packed, and, in some other axons, neurofilaments and neurotubules had disappeared. Rarely, the axolemma was filled with concentric laminated bodies, disintegrating mitochondria, or membranous profiles and finely granular material (Fig 3). Most nerves showed frequent denervated single Schwann cell processes or bands. Some Schwann cells had, within the cytoplasm, droplets of a substance ultrastructurally resembling fat.

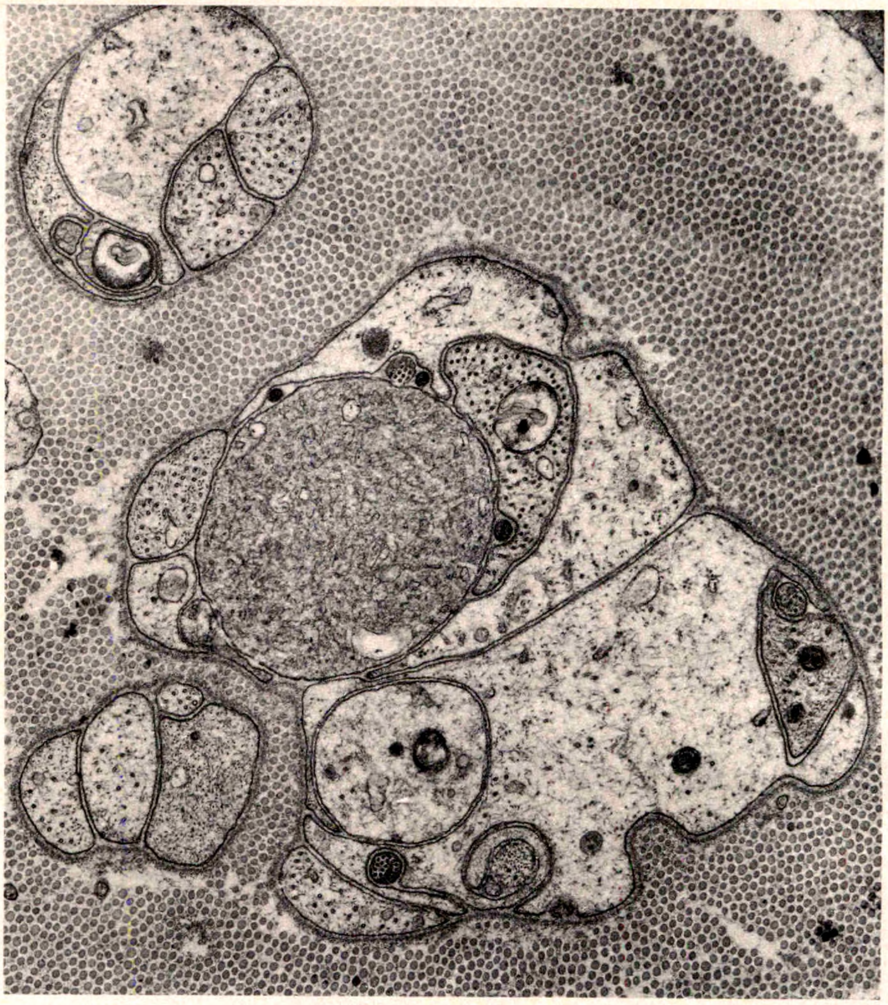
Fig 3.—Photomicrograph (case 2) showing large Schwann cell band containing several axons; some axons are normal. Note one contains folded membranous profiles, another is devoid of microtubules and microfilaments, but contains dense core granule (original magnification ×31,200).

The size frequency distribution of unmyelinated axons was determined in case 1 (Fig 4). The distribution was unimodal, but the peak occurred at about 1.0μ, being shifted to the left (normal peak at about 1.6μ).

Gas-Liquid Chromatography

The mean percentage area occupied by peaks A to I of elution curves from sural nerves of controls and patients were compared (Fig 5). No statistically significant differences in quantitative data nor in the appearance of peaks A to H could be detected. A statistically significant reduction in the size of peak I (cholesterol), however, was found in patient nerves.

COMMENT

All four patients were Navajo Indian children who showed nonprogressive impairment of neuromuscular development and severe sensory loss evidenced by corneal and cutaneous ulceration. In some, there was a modest elevation of cerebral spinal fluid protein. Electrodiagnostic studies confirmed the presence of neuromuscular disease. Morphologic examination of sural nerves showed almost total absence of myelinated fibers, with evidence of degeneration and regeneration of nonmyelinated axons. Findings from gas-liquid chromatography of the nerves were normal, except for marked decrease of the level of cholesterol in keeping with the morphologic paucity of myelin.

Different forms of mutilating neuropathies have been described in the literature. Their common underlying feature is profound sensory loss that leads to repeated injury and infections of limbs, with destruction of joints in some. The clinical diagnoses vary from Morvan disease to congenital indifference to pain, sensory radicular neuropathy, and congenital sensory neuropathy.[1] The cases may be isolated or familial. Except for the motor disorder, our patients resemble those with congenital sensory neuropathy. Most patients with congenital sensory neuropathy have normal strength. Both disorders are present in early life, and both are static. In both, the sural nerves show almost total absence of myelinated fibers. In congenital sensory neuropathy, this is attributed to failure of axonal growth or myelin formation.[4,5] In our patients, on the other hand, there was evidence of degeneration of myelinated fibers, and morphometric examination of unmyelinated fibers showed regeneration. Though on superficial clinical examination and on morphologic study of sural nerves the findings in our patients resembled those reported in hereditary sensory neuropathy, type II,[6] the severe motor disorder, corneal ulceration, and high level of cerebrospinal fluid (CSF) protein suggest that the syndrome described here is a distinct entity.

Hereditary sensory neuropathy may be associated with increase synthesis of IgA in the gastrointestinal tract.[7] We did not examine immunoglobulins in our patients, but they differ clinically. Patients with dysglobulinemia and sensory neurop-

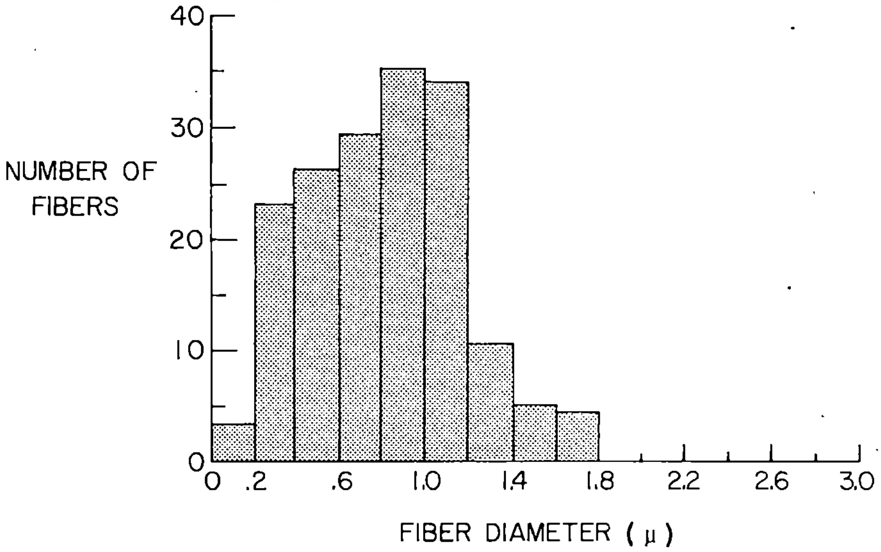

Fig 4.—Size frequency distribution of unmyelinated axons (case 1). Shift of curve to left present (normal peak at about 1.6μ).

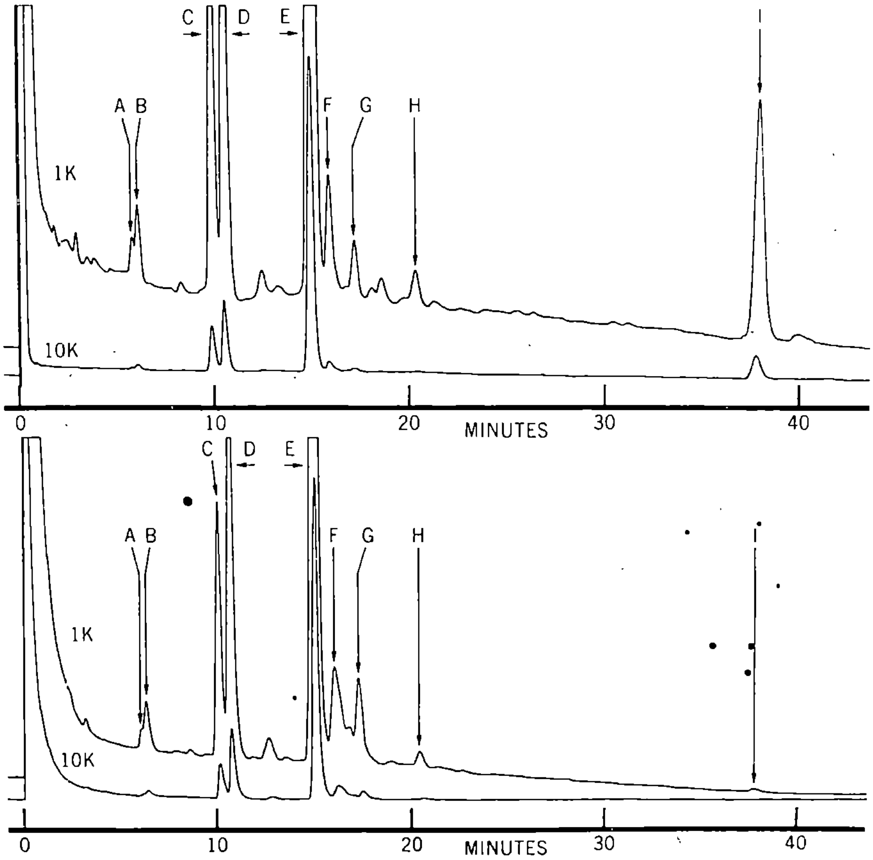

Fig 5.—Gas-liquid chromatograms. Top, Normal sural nerve from 7-year-old subject. Bottom, Sural nerve from patient 2. Peaks A through H identical in shape and area. Marked decrease in peak I (bottom) reflects almost total absence of myelin (10 K = 10× decrease in sensitivity of recording instrument).

athy were normal in childhood and adolescence, later developing distal hypalgesia and thermal hypesthesia, with ulceration and a normal level of CSF protein.

Though our patients also resembled some types of indifference to pain, they had impairment of all modalities of sensation rather than pain only. Moreover, the histology of nerves is clearly different. In indifference to pain with peripheral nerve lesions, there is involvement of both myelinated and unmyelinated fibers.[8] In other patients suffering from congenital insensitivity to pain, clinical and electrophysiologic evaluation of the peripheral nervous system has been normal. The indifference to pain is attributed to functional abnormality of the reticular formation and dorsal horns of the spinal cord.[9]

Two siblings were affected in one family. This does not constitute proof that the disease is genetically determined, but it seems likely that the disorder is either recessively inherited or, perhaps, dominantly inherited with incomplete expression. Although the illness was clearly present from the earliest observable age, it is difficult to be certain whether the process started in utero. While appearing static clinically, there was morphologic evidence of slow progression. In the earlier stages, as in the younger patients, degeneration of myelinated fibers was clearly evident. Later, almost all myelinated fibers were destroyed, and degeneration continued in nonmyelinated axons, many of which showed evidence of regeneration. Regenerative efforts of the myelinated fibers were absent. With the exception of two small myelinated fibers, a few large Schwann cell bands, and clusters of Schwann cells of complementary shape, there was little to suggest that myelinated fibers were ever present in the nerves from older patients.

Ultrastructural aspects and quantitative data on densities and sizes of myelinated and unmyelinated fibers have been reported[10] in normal sural nerves. Similar analysis in our patients showed chronic progressive degeneration, with total failure of regeneration of myelinated fibers and sprouting of unmyelinated axons as evidence of regeneration. This contrasts with indifference to pain, in which there is regeneration of both myelinated and unmyelinated fibers.[8] A common finding in chronic neuropathies is "onion bulb formation," but this was not found in our cases. It has been suggested that repetitive demyelination and remyelination is the cause of onion bulb formation. The absence of "onion bulbs" is, therefore, consistent with lack of remyelination.

The extent of peripheral nerve involvement in this apparently unique, genetically determined syndrome must, however, await more extensive sampling of the nervous system.

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Single-Agent Chemotherapy of Brain Tumors

A Five-Year Review

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• Identification of effective single chemotherapeutic agents for brain tumors must precede the rational use of multiple drug combinations. In phase 2 trials beginning in 1968, 158 patients with intrinsic brain tumors (mostly recurrent malignant astrocytomas) were considered evaluable.

The larger trials with more effective drugs produced these results: carmustine (BCNU) response rate, 47%, with median duration of nine months; lomustine (CCNU), 44%, with median duration of six months; procarbazine hydrochloride, 52%, with median duration six months; carmustine and vincristine sulfate combined, 44%, with median duration of only four months; and BIC (5-[3,3-bis(2-chloroethyl)-1-triazeno]imidazole-4-carboxamide), 38%, with median duration of five months. Administration of glucocorticoids was not found to bias the frequency of response.

Forty-seven patients, 26 of whom had responded to the initial drug, received a second drug. Among 26 patients who were evaluable, only four responded to the second drug.

(*Arch Neurol* 33:739-744, 1976)

Despite the use of adrenal glucocorticoids and refined diagnostic techniques, improvement in long-term survival of patients harboring malignant primary or metastatic brain tumors has been negligible. Glioblastoma multiforme, the most common of primary brain tumors, remains essentially incurable despite maximal surgery and radiation therapy. Chemotherapy offers new opportunities for treatment of malignant brain tumors, even though they reside in a pharmacological sanctuary, and their kinetic characteristics and location in a close compartment, the skull, pose special problems.[1-11]

Our brain tumor chemotherapy program was established to identify effective agents. As we move into combination chemotherapy, it seems appropriate to review our total experience with single agents, using uniform criteria to allow comparability of results observed with different drugs. The results differ from the original individual reports, because of both revision and standardization of criteria, and because of addition of more patients to these protocols.

SUBJECTS AND METHODS

Between July 1968 and March 1973, a total of 400 patients were admitted for consideration of chemotherapy for brain tumors. This review reports the results of 142 patients who were entered for their first oncolytic drug treatment and considered evaluable on single-agent phase 2 trials during that period, as well as those of 24 patients (16 evaluable, 13 first drug) treated in 1973 and 1974 in a phase 2 trial of BIC (5-[3,3-bis(2-chloroethyl)-1-triazeno]imidazole-4-carboxamide).

Criteria for Phase 2 Studies

Chemotherapy studies may be divided into three major types, or phases. Phase 1 studies involve patients with tumors treated with progressively increasing doses of a drug to establish the maximum safe dosage level for human beings. Phase 2 studies involve treatment of patients with a specific type of tumor with a given drug, and evaluation of whether the drug has an effect on that tumor, ie, whether the tumor shrinks or continues to grow. Phase 3 studies are randomized and controlled to compare groups of patients receiving the drug in question against other drugs or no drugs to measure prolongation of life or of disease remission.

A phase 2 study, thus, is the primary effort to identify which oncolytic drugs might be effective against a given tumor. In some tumors, the effect can be measured directly, such as blood cell counts for leukemia or the physical dimensions of the tumor in cutaneous lesions or on chest roentgenogram. In the brain, there is no means of such accurate measurement. All measurements of tumor mass, such as clinical condition, brain radionuclide imaging, or angiogram, are approximate and subject to error by changes, for example, in cerebral edema or blood brain barrier.

The following criteria for admission to

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and evaluation of phase 2 studies at this institution were established as the best available approximation:

1. The presence of an intracranial tumor, either proved histologically or with roentgenographic evidence sufficiently convincing to support no other diagnosis. All histological material and earlier diagnostic studies were reviewed by us.

2. Progressive neurological deterioration.

3. A mass (often more than one in the case of metastatic tumors) identified and measurable by brain scan, by contrast studies (angiography and pneumography), or by both. The majority of patients had increased intracranial pressure, but this was not a requirement.

4. If radiotherapy had been administered, a period of at least three months separated the completion of irradiation and the institution of chemotherapy.

5. In the small number of cases when a patient had received prior chemotherapy, we waited at least six weeks before starting therapy. If the previous drug had been given in therapeutic doses, the new chemotherapy was considered a second drug trial; if the doses were considered nontherapeutic (inappropriately low), the same interval was required, but the new treatment was considered a first drug trial. Included in this latter group were three patients treated postoperatively by direct injection of methotrexate sodium into the tumor bed. They exhibited progressive deterioration three months or more after the last injection and were assigned to first drug studies.

6. Life expectancy of at least two months; patients were not further stratified according to stage of disease.

7. Informed consent to participate in clinical trials approved by our institutional

between the completion of radiotherapy and symptomatic regrowth of tumor ranged from 3 to 18 months in most cases. Postmortem examination confirmed the diagnosis in the great majority of cases. Five diagnostic mistakes were discovered, however, causing elimination of those patients from the study. One had received postoperative radiotherapy after histological verification of a brain stem astrocytoma. Although he had neurofibromatosis, unsuspected bilateral tumors of the eighth nerve caused his death. Three patients had fatal radionecrosis of one or both cerebral hemispheres and no identifiable tumor at the time of death. One patient died as a direct result of multiple arterial occlusions and cerebral infarction, with clinically insignificant residual tumor.

Histologically Unverified Tumors

These were patients believed beyond reasonable doubt to harbor brain tumors, either primary or metastatic. In all instances, neuroradiologic procedures provided unequivocal evidence of a mass, the history and neurological examination indicated the presence of a tumor, and, in our opinion, the available evidence supported no alternative diagnosis, such as radiation necrosis or brain abscess. Postmortem examination was performed eventually in 90% of patients with unverified tumors, and a tumor was then verified in every instance.

Primary tumors in the unverified category occupied one of three sites: brain stem, deep midline (basal ganglia and corpus callosum), and motor cortex of the dominant cerebral hemisphere. All supratentorial intrinsic tumors in patients 35 years of age and older were assumed to be malignant gliomas, and in only one case (reticulum cell sarcoma of the corpus callo-

aminase, lactic dehydrogenase, and glucose; brain scintiphoto (Technetium Tc99m-pentetic acid); electroencephalogram; neuroradiologic contrast studies (cerebral angiography in all cases and pneumography when required for delineation of the tumor); cytologic examination of cerebrospinal fluid in selected cases (medulloblastomas, ependymomas, and suspected leptomeningeal carcinomatoses); and formal psychometric evaluation of patients with frontal and temporal tumors when routine neurological examination failed to provide more easily measured functional deficits.

Follow-up Evaluations

All patients were referred back to the care of the referring physician(s). Twice weekly blood cell counts and chemistry studies as required by protocol were obtained, the results being transmitted to the chemotherapy nurse by telephone or mail. Unless a patient's condition required admission to hospital, no interim neurological evaluation was obtained between treatments.

Before starting each subsequent course of treatment, all patients were readmitted to the hospital for reevaluation. Complete examinations and all studies performed in the initial evaluation, with the exception of neuroradiologic contrast studies, were repeated. Early in the period covered by this review, contrast procedures, usually angiography, were repeated as a part of each evaluation, but subsequently, because of their limited value in determining drug responsiveness, we reserved their use for those situations requiring a change in treatment, ie, either operative intervention or crossover to another chemotherapy protocol.

[redacted]

Table 1.—Drug Dose and Schedule

Drug	Dose	Method	Schedule
Carmustine	80-90 mg/sq m	Intravenously 3 times	Every 6-8 wks
Lomustine	120-130 mg/sq m	Orally once	Every 6-8 wks
Dacarbazine	200-300 mg/sq m	Intravenous push 9 times	Every 6 wks
	200-250 mg/sq m*	Intravenous push 5 times	Every 6 wks
Carmustine + vincristine sulfate Carmustine	80 mg/sq m	Intravenously 3 times	Every 6-8 wks
Vincristine sulfate	0.05 mg/kg/wk	Intravenous push	Every week
	2 mg/sq m*	Intravenous push	Every week
Procarbazine hydrochloride	150 mg/sq m	Orally every day 30 times	Every 2 mo
Belomycin sulfate	15 mg/sq m	Subcutaneously	Every 4 days for 6 wks
BIC	900 mg/sq m	Intravenously 5 times	Every 6 wks

*Dosage reduced for toxicity.

cording to uniform criteria (described below). Consequently, response rates reported here differ, although not significantly, from results previously published.[2,3,5,8,9]

Evaluability

Not all patients treated with a drug were considered to be evaluable; ie, the response of a tumor to a drug could not always be determined. To be evaluable, a patient must have fulfilled all phase 2 criteria, have completed one full course of chemotherapy, and lived for at least two months after initiation of therapy. Obviously, this eliminates from consideration some patients whose disease did not respond to treatment. However, it is felt that since the question of the study is the effect of the drug on this tumor, rather than on survival, the drug must have adequate time to demonstrate an effect to be evaluated. Since the effect of a drug on tumor size is delayed, especially in the brain,[12] a patient with a very large tumor could have received a drug that had a good effect on the tumor, yet still die before the tumor actually shrinks. In addition, this criterion reduces bias that might be introduced between different studies by the aggressiveness of the investigators at that time (ie, if more very sick patients with rapidly advancing tumors are entered on a particular study, the response rate might be unduly depressed in comparison with another study).

A small number of patients considered evaluable in earlier reports were designated nonevaluable by present criteria. Reasons for nonevaluability and the number of patients in each category are detailed below:

Basis for Nonevaluability	No. of Patients
Survival less than 2 mo after beginning treatment	53
Neurological condition not clearly deteriorating immediately prior to treatment	7
Failure to complete 1 full course of therapy	5
Survival beyond 2 mo, but accurate follow-up information not obtainable	5
Total	**70**

Response to Treatment

In determining the oncolytic effectiveness of an agent, we assigned first importance to the neurological examination. The functional state (eg, Karnofsky rating) was not considered as important, as it can be affected by so many extraneous factors (eg, physical therapy, infections, and social conditions). The correlation between clinical improvement and an improved scintiphoto is good, but imperfect.[13] We use the scintiphoto as a second indicator of drug effect for the following reasons: (1) an improved scintiphoto may precede neurological improvement, and vice versa; (2) in neurologically "silent" areas, eg, frontal pole, neurological examination may provide little clinical indication of change in tumor mass; and (3) certain neurological deficits, such as hemianopsia, may be irreversible, and real tumor regression may be accompanied by no improvement in neurological function. Angiography, on the other hand, was found to have only limited value as an indicator of tumor regression,[14] and, because of morbidity and expense, it was not used routinely after the first year. Computerized tomography is now proving useful, but was not available at the time of these studies.

Evaluable patients were assigned to one of three categories of response on the basis of a review of two or more recorded neurological examinations and corresponding brain scintiphotos.

A *responder* had unequivocal neurological improvement *and* brain scans demonstrating a small area of abnormal permeability. (Changes of intensity of uptake are of unknown value and were not counted.) Where multiple tumors were present, shrinkage of one tumor and stability of the other(s) was acceptable.

The category of *probable responder* involved two types of response: (1) unequivocal improvement in neurological condition and stable brain scintiphoto, or the reverse; and (2) in malignant tumors (glioblastoma, malignant astrocytoma, medulloblastoma, and cerebral metastases), arrest of a previously deteriorating course, with stability of findings from neurological examination and scintiphoto for at least three months.

A *nonresponder* failed to meet the above criteria. These categories must be qualified by the use of steroids. Dexamethasone was used to combat neurological deterioration when a patient's functional capacity was severely compromised. If the patient was receiving corticosteroids at the time of initiation of chemotherapy, the minimal maintenance dose required to achieve the desired clinical state was defined; when that dose had been maintained for 48 hours or more, new baseline examination and scintiphoto were obtained. No patient was considered a responder or probable responder on the basis of evaluation at the end of a course if steroid dose had been increased and maintained since two weeks before the onset of that course. Improvement between beginning and end of the course should not be attributable to increased steroid antiedema effect.

Although glucocorticoids inhibit the growth of a murine glioma,[15] we have assumed that they possess no antitumor activity in man, and that clinical improvement after their use was ascribed to known antiedema properties. In earlier studies, a notable reduction of required steroid was used as an indication of tumor regression. While this criterion is probably valid, it was not used in the present review. In most of those patients with tumors responding by other criteria, however, maintenance steroids were decreased without ill effect.

In an effort to determine the contribution of glucocorticoids to chemotherapeutic responsiveness, we analyzed 178 consecutive patients who had not previously been treated with chemotherapy. Of the 178 patients, 84 had never received steroids; 94 had received steroid treatment at least from the beginning of chemotherapy. Each group had 28% responders; the steroid group had 10%, and the nonsteroid group had 6% probable responders (Table 2). We believe that concomitant administration of steroids does not bias the evaluation of chemotherapeutic effectiveness, and that the data do not support the notion that steroids have synergistic action or oncolytic activity.

Table 2.—Frequency of Response With and Without Concomitant Administration of Adrenal Corticosteroids

	% of Patients Treated	
	With Corticosteroids (N = 94)	Without Corticosteroids (N = 84)
Responders	28	28
Probable responders	10	6
Nonresponders & nonevaluable	62	66
Total	**100**	**100**

Table 3.—First Drug Responses

Drug	Total No. of Evaluable Patients	No. (%) of Responders	Median Duration of Response, mo
Carmustine	57	27 (47)	9
Lomustine	36	16 (44)	6
Procarbazine hydrochloride	27	14 (52)	6
Carmustine + vincristine sulfate	22	10 (45)	4
BIC	13	5 (38)	5

RESULTS

Treated and Evaluable Patients

In the following analysis, first drug responses are described separately from responses to a second drug. Because there was no difference in the responsiveness of glioblastomas and anaplastic astrocytomas, they are combined under malignant astrocytomas (corresponding to grades 3 and 4 astrocytomas). The few astrocytomas lacking anaplastic features are considered separately. We are aware of the histological variability among brain stem gliomas, and at least two in our series were frank glioblastomas. Yet, because of the small number of brain stem tumors, they were considered together. Melanomas constitute one category of metastatic tumors; in the other category were primary lung tumors or undifferentiated tumors of unknown primary origin. One protocol involving a combination of carmustine (BCNU) and vincristine sulfate was included in the present review, because the results approximated the results with carmustine alone. Finally, probable responders are added to unequivocal responders in calculating maximum response rates. For each drug, the number of probable responders was small, and in no instance did the number exceed 10% of evaluable patients in that series.

The response to different drugs given as a patient's first course of chemotherapy is shown in Table 3. The overall response rates to lomustine (CCNU), carmustine alone, and carmustine with vincristine were remarkably similar (44%, 47%, and 45%, respectively). The response rate to procarbazine hydrochloride was insignificantly greater (52%). The response rate of BIC was slightly less, 38%. The median duration of response was six months for both lomustine and procarbazine. The median duration of response of nine months for carmustine reflects many more long-term survivors, two of whom are alive without evidence of the disease after four years. The shorter median response (four months) for carmustine-vincristine was unfavorably biased by three brief responses in patients with metastatic melanomas and the absence of any long-term survivors among the malignant astrocytomas. Median response for BIC was five months.

Table 4 contains the second drug responses, ie, those patients who had been previously treated with another form of chemotherapy. As a clinical group, their condition, general and neurological, was less favorable. Only four of 26 evaluable patients responded to the second drug; one of whom failed to improve, but is alive and stable two years after treatment; another was a probable responder; a third had a progressive tumor for which a biopsy specimen was not obtained; the fourth had previously

Table 4.—Second Drug Responses*

Drug	Total No. of Evaluable Patients	No. of Responders
Carmustine	1	0
Lomustine	6	0
Procarbazine hydrochloride	3	0
Carmustine + vincristine sulfate	2	1†
Bleomycin sulfate	3	0
Dacarbazine	8	1‡
BIC	3§	2‖

*A total of 26 (55%) of 47 patients had responded to the first drug.

†Patient (with malignant astrocytoma) unimproved, but living; condition stable two years after treatment.

‡Probable responder (with glioblastoma).

§Four patients not evaluable because of early death.

‖One responder for two years with a tumor for which a biopsy specimen was not obtained; one responder with a glioblastoma. Both had previous drug discontinued for reasons other than tumor regrowth. Regrowth and start of BIC therapy six and four months, respectively, after first drug discontinued.

Table 5.—Drug Response by Tumor Type

	No. of Responders/No. of Evaluable Patients					
Tumor	Carmustine	Lomustine	Procarbazine Hydrochloride	Carmustine + Vincristine Sulfate	BIC	Total
Malignant astrocytoma	20/40	10/22	10/20	6/12	2/8	**48/102**
Low-grade astrocytoma	1/3	1/1	...	...	1/3	**3/7**
Brain stem glioma	2/3	0/1	...	1/5	...	**3/9**
Oligodendroglioma	...	0/1	0/1	...	1/1	**1/3**
Medulloblastoma	0/1	1/1	3/4	...	...	**4/6**
Ependymoma	3/6	0/3	0/1	...	...	**3/10**
Metastatic melanoma	1/1	...	...	3/5	...	**4/6**
Other metastatic	0/3	4/7	1/1	...	1/1	**6/12**
Total	**27/57**	**16/36**	**14/27**	**10/22**	**5/13**	**72/155**

been treated with only one course of carmustine. The first drug had been discontinued for the third and fourth patients for reasons other than tumor progression. The high proportion of nonevaluable patients reflects early deaths. Often, these patients also could not tolerate usual doses of the second drug regimen.

First drug responses by tumor type are contained in Table 5. For malignant astrocytomas, the response rates to the nitrosoureas and procarbazine were almost identical at 50%, while BIC achieved only 25%. Although the number of patients is small (three of four), procarbazine proved effective for medulloblastoma, which is supported by recent experience with a three drug combination including procarbazine. Three of six patients with ependymomas responded to carmustine, and one patient is alive and free of tumor after two years of continuous therapy and three additional years without treatment.

The reported effectiveness of carmustine against melanoma[16] finds support in our small number of patients. Possibly, vincristine enhances the effectiveness of carmustine against melanoma within the CNS, but our experience is very limited. While the numbers are again small, lomustine produced striking clinical regressions in some patients harboring intracranial metastases from primary pulmonary tumors.

Toxicity

A detailed consideration of drug-related complications is beyond the purpose of this review. This information is available in earlier brain tumor chemotherapy reports and in published reports covering the use of the same agents against nonneural tumors.[1-9] Patients harboring intracranial tumors have neither more nor less liability than patients receiving the same drugs for tumors of other sites.

With the exception of vincristine, these drugs exert their major toxicity in the hematopoietic system, principally platelet and granulocyte precursors. While platelet counts below 50,000/cu mm and white blood cell (WBC) counts below 3,000/cu mm were common, only five patients required platelet transfusions; all recovered. Only three patients died as a direct result of uncontrolled infection during periods of granulocytopenia. Patients with WBC counts below 1,500/cu mm have been placed in protective isolation, but antibiotics have been administered only to those patients with overt infection or unexplained fever.

Some degree of peripheral neuropathy appeared in the majority of patients receiving more than four doses of vincristine. In no instance was the neuropathy disabling, and in most cases it was reversible after the vincristine was stopped.

Cumulative bone marrow depression, typically manifested by chronic granulocytopenia, followed the administration of the nitrosoureas and procarbazine. Seldom could we administer any of these agents at full doses for more than four courses. The nadir for granulocytes occurred four weeks after the administration of carmustine and lomustine, and six weeks after beginning the 28-day course of procarbazine. In a few patients, granulocytes recovered only to fall again two weeks later, ie, at the time the next course was to begin. Retreatment was sometimes delayed by these secondary falls, but more often by sustained initial leukopenia.

Cumulative bone marrow toxicity affected primarily responding patients, nonresponders receiving fewer courses. Irradiation of the spinal axis, as for medulloblastoma, potentiates this problem.

COMMENT

The identification of oncolytic agents clinically effective against primary and metastatic tumors constitutes an essential step in the sequential evolution of brain tumor chemotherapy. In the present report, we have reviewed an experience with phase 2 studies of single agents, hoping that what we have learned will be of value to others designing phase 2 protocols for brain tumor chemotherapy. While the search for more effective single agents should continue, the present information can be extended in at least two directions: more effective drug schedules and combination chemotherapy.

Until recently, combination chemotherapy for brain tumors seemed premature. In the first place, the desired pharmacologic characteristics of potentially useful agents were unknown. Furthermore, the rational design of a combined drug protocol assumes the availability of agents possessing some activity when used alone. Although the chance combination of two or more untried drugs might prove to be effective, the odds weigh heavily against it.

Although this review emphasized single drugs, we have included our limited experience with vincristine and carmustine in combination, two drugs with established effectiveness against neural tumors, yet with differing toxicity. The combination, while logical, proved to be no more effective than carmustine used alone, and, subsequently, we obtained the same result in experiments using a rat glioma model (unpublished data). In contrast to the disappointment of carmustine and vincristine, a limited experience with the combination of procarbazine, lomustine, and vincristine has been highly encouraging. With the small number of active agents presently identified, the number of combined drug protocols is restricted. Consequently, an effort to identify effective agents must continue.

The current interest in brain tumor chemotherapy becomes reasonable in the light of successes reported by chemotherapists working in other organ systems. The oncologist interested primarily in the CNS can apply available knowledge in approaching tumors that obey a different set of rules because of their peculiar environment. The future course of brain tumor chemotherapy seems reasonably clear, and, in the light of modest success achieved with active single agents, guarded optimism seems justified.

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Nonproprietary Names and Trademarks of Drugs

Vincristine sulfate—*Oncovin.*
Bleomycin sulfate—*Blenoxane.*

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Adjuvant Nitrosourea Therapy for Glioblastoma

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• An attempt was made to evaluate the potential advantages of chemotherapy in the treatment of 62 patients with glioblastoma. Twenty-four of the 62 patients received adjuvant nitrosourea chemotherapy with carmustine (BCNU), lomustine (CCNU), or semustine (methyl CCNU) in addition to surgery and radiotherapy. Thirty-three of the 62 patients were involved in a controlled, prospective, randomly allocated study. Quality or quantity of survival was not prolonged in patients who received chemotherapy. Age greater than 64 years, a severe postoperative neurological deficit, or the onset of symptoms less than 12 months prior to surgery were associated with a worse prognosis. The valid evaluation of the effect of a form of treatment on survival in patients with glioblastoma is contingent on the rigorous avoidance of preselected factors that may predispose the treated group to a more favorable prognosis.

(*Arch Neurol* 33:745-750, 1976)

Laboratory and clinical studies suggest that the lipid-soluble nitrosoureas (carmustine [BCNU], lomustine [CCNU], and semustine [methyl CCNU]) may be effective in the treatment of malignant brain tumors[1-11] We have evaluated this suggestion since 1970 in a prospective, controlled, randomly allocated clinical study.

SUBJECTS AND METHODS

The study included 62 consecutive patients, with verified glioblastoma (Kernohan grade 3 or 4) for which a diagnosis was made and biopsy specimen obtained for the first time between Jan 1, 1970, and Dec 31, 1972, without prior radiotherapy or chemotherapy. An internal decompression was done when the tumor was in a nonvital area and it was believed that this could be done without worsening neurological function. Reoperation was performed in 15 patients for tumor recurrence when the patient had a functionally useful remission for at least ten months after the initial surgery. No patient had more than two craniotomies. Within four weeks after surgery (usually within ten days), randomization to either x-ray therapy alone or x-ray therapy plus chemotherapy was offered to patients who appeared likely to survive the six-week period required for radiotherapy. Not all patients who qualified were willing to be randomized. Informed consent was obtained in each case after risks and possible benefits of the study protocol and alternative forms of treatment were explained to the patient and the responsible relatives. For those patients who consented to randomization (33 cases), the anticipated treatment modality of radiotherapy alone (16 cases) or radiotherapy plus chemotherapy (17 cases) was determined by a sealed envelope technique. Not all of the randomized patients received a full course of radiotherapy because of rapid clinical deterioration. A full course of radiotherapy consisted of 3,000 rads to the whole brain in three weeks, followed by an additional 3,000 rads to the tumor; a cobalt 60 unit was used. Radiotherapy was initiated within four weeks (usually ten days) of surgery. Twelve patients who did not receive chemotherapy were given hyperbaric oxygen during the last 3,000 rads of their radiotherapy. Nitrosourea chemotherapy was started within four weeks of surgery (usually ten days) in patients who were randomized to receive this adjuvant form of treatment.

Patients with glioblastoma who began chemotherapy in 1970 were given carmustine intravenously (100 mg/sq m) daily for two days, which was repeated every six to eight weeks. Those who started chemotherapy in 1971 received an orally administered dose of lomustine (100 mg/sq m) once every six to eight weeks. When chemotherapy was initiated in 1972, semustine, which had a superior effect against certain animal tumor models,[12] was given orally (150 mg/sq m) once every six to eight weeks. When leukopenia (white blood cells [WBCs] ≤ 3,200/cu mm) or thrombocytopenia (platelets ≤ 75,000/cu mm) developed, the subsequent chemotherapy was reduced to two thirds of the original dose. Chemotherapy was stopped when the illness became terminal.

Patients who received chemotherapy had a complete blood cell count and platelet count each week. Every eight weeks the following laboratory determinations were obtained: calcium, inorganic phosphorous, glucose, urea nitrogen, uric acid, cholesterol, total protein, albumin, total bilirubin, alkaline phosphatase, lactic dehydrogenase, and glutamic oxalcacetic transaminase. Skull x-ray films, echoencephalogram, electroencephalogram, and brain scan (mercury 197) were performed on all patients every 16 weeks, or earlier if clinical deterioration occurred. Patients were seen every six to eight weeks, and a complete neurological examination and functional status evaluation were done at that time.

Survival was determined from the day of tissue diagnosis of glioblastoma to death. Patients were divided into three groups for analysis. Group A (62 patients) represents the entire consecutive series of tissue-verified glioblastoma; 22 of these patients did not complete a full course of radiotherapy. Group B (40 patients) includes those who had surgery and completed a full course of radiotherapy (6,000 rads, except two patients who received 5,080 and 5,400 rads) that was started within four weeks (usually ten days) of surgery. Group C (33 patients) is comprised of those who were randomized soon after surgery to receive either chemotherapy and radiotherapy (17 patients) or radiotherapy alone (16 patients). When group C results were tabulated, a patient was considered to be in the original treatment group to which he or she was randomized, whether or not a full course of that treatment was given. Thus, not all patients in group C received a full course of radiotherapy, and of those who were randomized to receive radiotherapy and chemotherapy, four did not receive chemotherapy because of a rapidly deteriorating clinical condition. A separate analysis was done on these patients who were

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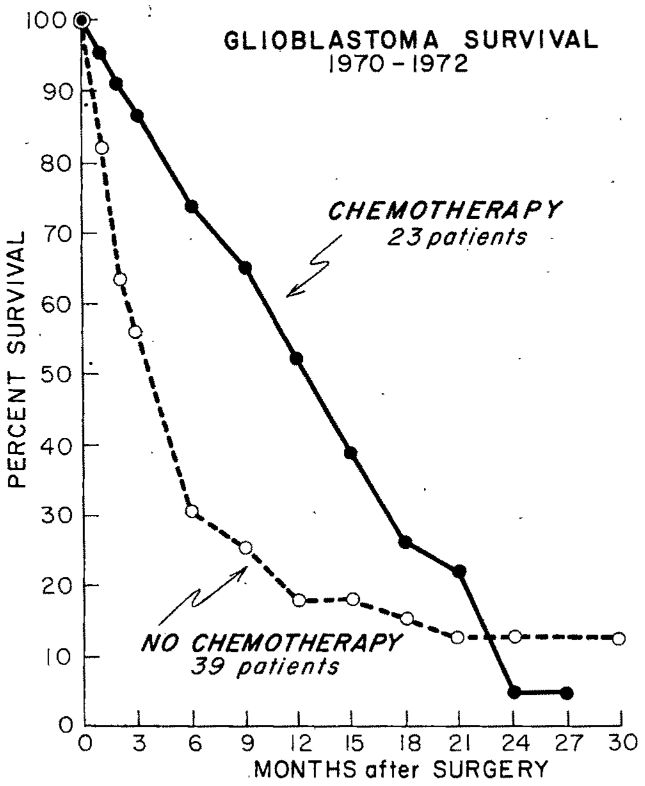

Fig 1.—Survival data for group A glioblastoma patients. False impression of benefit from chemotherapy obtained because many patients with poor prognosis were not given chemotherapy.

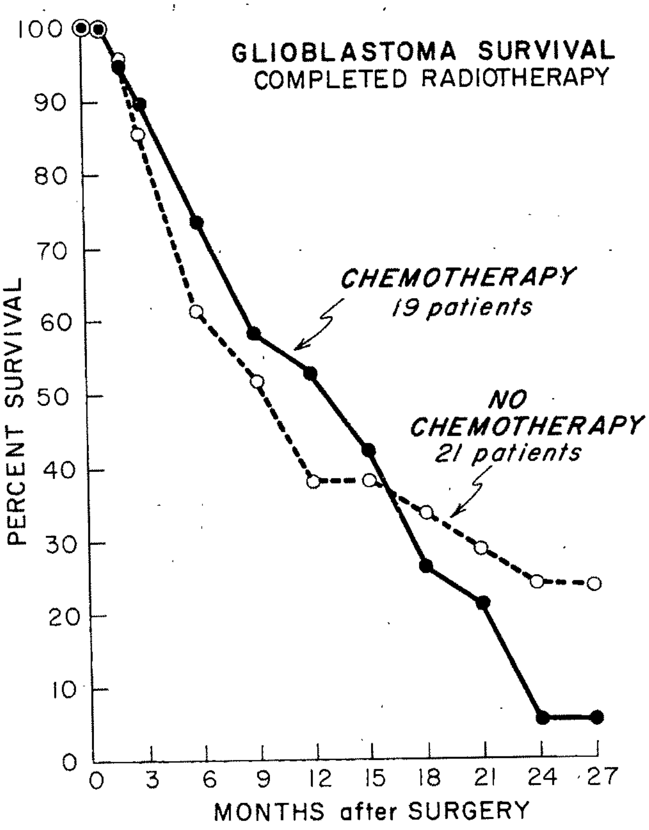

Fig 2.—Survival data for group B glioblastoma patients. All patients completed at least 5,000 rads of radiotherapy.

randomized and who completed a full course of radiotherapy (12 patients) or a full course of radiotherapy and at least one course of chemotherapy (12 patients).

RESULTS

Group A

Of a consecutive series of 62 patients with glioblastoma, 50% lived for more than 5.4 months. Six (9.7%) were alive more than two years after initial surgery (Fig 1). One of these patients had received radiotherapy and chemotherapy (Semustine, 150 mg/sq m every six to eight weeks for four courses and 100 mg/sq m every six to eight weeks for ten courses) and was reoperated on for recurrent tumor 26 months after initial surgery; he died four months later. Five of the other long-term survivors had been treated by surgery and radiotherapy alone without adjuvant chemotherapy. One of these patients, a 7-year-old boy, was living and well without evidence of recurrence 31 months after initial surgery. Two men were reoperated on for a cystic recurrence at 16 and 35 months after primary surgery and were still alive with mild neurological deficit 34 and 36 months after initial tissue diagnosis. Two other men were alive without clinical recurrence at 33 and 34 months after initial surgery.

In group A, there were 23 patients who received chemotherapy; 50% lived for more than 12 months, and one (4%) survived for more than 24 months (Fig 1). Thirty-nine patients did not receive chemotherapy; 50% lived more than 4.2 months, and five (13%) survived for more than 24 months. An analysis of other factors that might have influenced survival showed three patients who were at least 65 years old and three patients with a severe neurological deficit (7 to 14 days after surgery) in the chemotherapy group; there were 15 patients who were at least 65 years old, and 18 with a severe postoperative deficit in the nonchemotherapy group (Table 1).

Group B:

Nineteen glioblastoma patients who completed a full course of radiotherapy were also given chemotherapy; 50% were alive after 12 months, and one (5%) survived for more than 24 months (Fig 2). There were 21 patients who completed radiotherapy, but did not receive chemotherapy; 50% were living after nine months, and five (24%) were alive after 24 months. These differences in survival, as well as differences in quality of survival (Tables 2 and 3) between the chemotherapy and nonchemotherapy groups, are not significant to the $P = .05$ level. There were a few more patients who were older than 64 years (five patients) in the nonchemotherapy than in the chemotherapy group (three patients) (Table 1). There were more patients with onset of symptoms at least 12 months prior to surgery (six patients) in the nonchemotherapy group than in the chemotherapy group (three patients).

Group C

Seventeen patients were randomized to receive chemotherapy in addition to surgery and radiotherapy. Three of these patients died before they were able to complete a full course of radiotherapy. Two of these patients who were very ill after randomization and a third patient, who completed 5,400 rads of radiotherapy but had an unexplained fever, were never given chemotherapy, even though they were randomized to receive it. Four patients who were randomized to radiotherapy alone

Table 1.—Factors That Might Influence Survival

	Group A		Group B		Group C	
	Chemotherapy (N = 23)	Nonchemotherapy (N = 39)	Chemotherapy (N = 19)	Nonchemotherapy (N = 21)	Chemotherapy (N = 17)	Nonchemotherapy (N = 16)
Age						
Median, yr	51	62	51	56	49	56
No. of patients aged 65 yr	3	15	3	5	3	3
Range, yr	5-70	7-78	16-70	7-73	16-73	31-69
Sex						
No. of male patients	16	26	13	11	13	10
No. of female patients	7	13	6	10	4	6
No. of patients randomized for therapy	14	18	13	13	17	16
Onset of symptoms						
Median, mo prior to surgery	3	2	3	3	3	3
No. of patients with onset 12 mo prior to surgery	3	7	3	6	2	5
No. of patients with severe neurological deficit*	5	18	3	2	4	4
Histological grade						
No. of patients with grade 3	9	17	8	10	10	7
No. of patients with grade 4	14	22	11	11	7	9
No. of patients with large decompression	19	27	15	15	12	9
No. of operations performed†	26	41	22	23	20	18
No. of patients receiving 6,000 rads	21	20‡	19	21‡	14§	12
No. of patients receiving O_2	0	12	0	12	0	11
No. of patients receiving carmustine	6	0	4	0	1‖	0
No. of patients receiving lomustine	9	0	7	0	6	0
No. of patients receiving semustine	8	0	8	0	6	0

*First week after surgery.
†No patient had more than two craniotomies.
‡One patient received 5,400 rads; one received 5,080 rads.
§One patient received 5,400 rads.
‖Four patients who were randomized to receive chemotherapy did not receive it because of rapidly deteriorating clinical course.

Table 2.—Chemotherapy and Survival

	Total No. of Patients	50% Survival, mo	P*
Group A			
Chemotherapy	23	12.0	<.005
Nonchemotherapy	39	4.2	
Group B			
Chemotherapy	19	12.0	>.300
Nonchemotherapy	21	9.0	
Group C			
Chemotherapy	17	6.1	.175†
Nonchemotherapy	16	6.3	

*Based on standardized Wilcoxin statistical test.
†Associated with a negative Wilcoxin statistic.

were unable to complete a full course of radiotherapy. There was no difference ($P > .3$) in quantity or quality of survival between those randomized to receive chemotherapy (50% alive after 6.1 months) and those randomized not to receive chemotherapy (Fig 3) (50% alive after 6.3 months, Tables 2 and 3). There were a few more patients (five patients) with a long preoperative symptom period in the nonchemotherapy subgroup than in the chemotherapy subgroup (two patients) (Table 1). Of the 12 patients who were randomized to radiotherapy alone and who completed a full course of radiotherapy, 50% were alive after 9.1 months. This was not significantly different ($P > .3$) from the other 12 patients who were randomized and who completed a full course of radiotherapy and at least one course of chemotherapy; 50% of these patients were alive after seven months.

Factors That Might Influence Survival

Several factors were analyzed to see if they correlated with prolonged survival (Table 4). A severe neurological deficit that was present between 7 and 14 days after surgery, patient age greater than 64 years, or the onset of symptoms less than 12 months before surgery was associated ($P < .05$) with a shorter survival. The size of operative resection, histological grade (3 or 4), or sex did not correlate with survival.

Toxicity (Group B)

All patients who received nitrosourea chemotherapy showed either

Table 3.—Quality of Survival

	No.(%) of Patients					
	Group A		Group B		Group C	
Good Survival*	Chemotherapy (N = 23)	Nonchemotherapy (N = 39)	Chemotherapy (N = 19)	Nonchemotherapy (N = 21)	Chemotherapy (N = 17)	Nonchemotherapy (N = 16)
> 6 mo	11(48)	9(23)	10(53)	10(48)	7(41)	6(38)
>12mo	7(30)	7(18)	7(37)	7(33)	6(35)	5(31)
>18 mo	2(9)	5(13)	2(11)	5(24)	2(12)	4(25)
>24 mo	1(4)	5(13)	1(5)	5(24)	1(6)	4(25)

*Functioning at a normal or near normal capacity.

Table 4.—Probability of Significance of Factors Affecting Survival

Factors	Total No. of Patients	50% Survival, mo	P*
Severe neurological deficit†			
Present	22	1.7	<.005
Absent	40	11.2	
Age			
≥65 yr	18	2.5	<.005
<65 yr	44	7.9	
Onset of symptoms			
≥12 mo prior to surgery	10	16.2	.038
<12 mo prior to surgery	52	5.0	
Sex			
Male	42	5.1	.280
Female	20	8.2	
Resection			
Small	13	4.8	>.300
Large	49	6.3	
Group B histological grade			
Grade 3	18	4.9	>.300
Grade 4	22	6.3	

*Based on standardized Wilcoxin statistical test.
†First week after surgery.

mild leukopenia (WBCs < 4,500/cu mm) or mild thrombocytopenia (platelets < 150,000/cu mm). More severe leukopenia (WBCs < 3,000/cu mm) was noted in two of four patients who received carmustine and three of seven patients who received lomustine, but in none of those treated with semustine. Marked leukopenia (WBCs < 2,000/cu mm) was noted in only one patient who was treated with carmustine; he also had severe thrombocytopenia (platelets < 30,000/cu mm). A 23- to 36-day delay for maximum bone marrow suppression was noted in all patients. Maximum toxicity occurred in subsequent courses in one half of patients who received at least two consecutive courses at the initial dose.

Mild nausea and vomiting occurred in 25% of patients and was easily controlled with antiemetic medication. Hepatitis developed in one patient (carmustine) and infection in one (carmustine). No drug-related deaths were identified.

COMMENT

A significant prolongation of survival was not seen in patients with glioblastoma treated with nitrosoureas, surgery, and radiotherapy, as compared with those treated with surgery and radiotherapy alone in groups B and C, but was seen in group A (Table 2). A comparison of other factors that might have affected survival showed no major differences in the chemotherapy and nonchemotherapy subgroups of groups B and C, but showed a preponderance of elderly patients and those with a severe postoperative deficit in the nonchemotherapy subgroup of group A (Table 1). Patients in group A who received chemotherapy were preselected for a more favorable prognosis, and, therefore, a comparison of survival in the chemotherapy and nonchemotherapy subgroups of group A is not valid.

Another reason for the lack of validity in comparing survival in the chemotherapy and nonchemotherapy subgroups of group A is the presence of primary as well as recurrent cases of glioblastoma in group A, and the use of recurrent cases (in four instances) as a method for selecting chemotherapy patients. Patients with recurrent glioblastoma have survived for a definite and sometimes prolonged period after initial surgery. They may be preselected for having a longer survival, when survival is computed from the time of initial surgery, regardless of the effectiveness of treatment given at the time of recurrence. (Recurrence was not a factor in selecting treatment in groups B and C. All patients in groups B and C had chemotherapy or radiotherapy or both initiated shortly after primary tissue diagnosis and operation).

Survival data from the entire group A may be compared with other consecutive series of histologically verified glioblastoma for which chemotherapy was not used at all (Fig 4). No significant difference could be detected between this series and the others. A suggestion of possible longevity in the present series was noted in comparison with some older series,[13-15] one of which antedated the use of antibiotics and radiotherapy.[13] The most valid historical control for the present series (group A) is one in which steroids, modern surgical technique, and radiotherapy were used.[16] Survival was not longer in the present series than in that one. The presence of many patients who did not receive chemotherapy in the present consecutive series (group A) might theoretically mask a possible beneficial effect of chemotherapy when historical con-

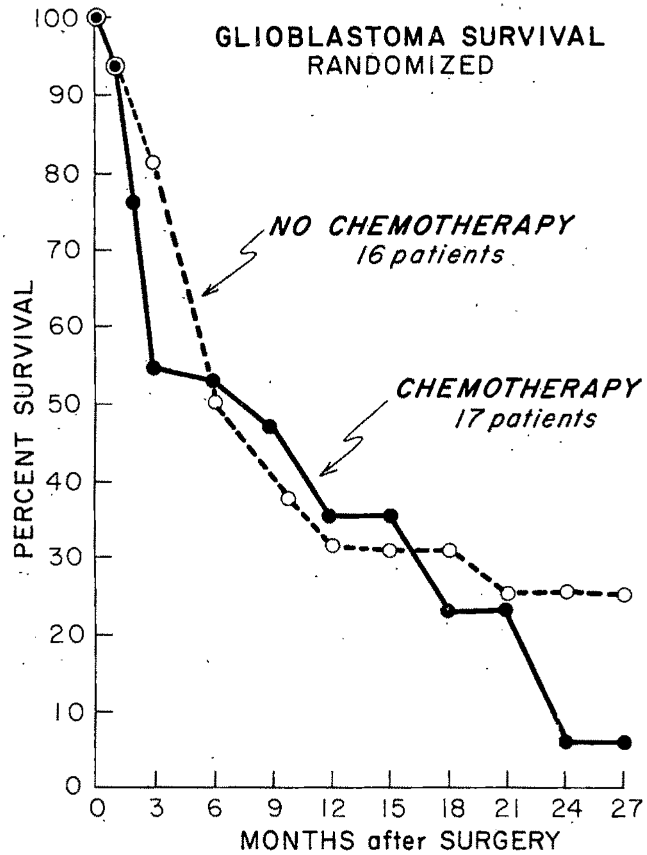

Fig 3.—Survival data for group C glioblastoma patients. One week after surgery, all patients randomized to either radiotherapy alone or radiotherapy plus nitrosurea chemotherapy.

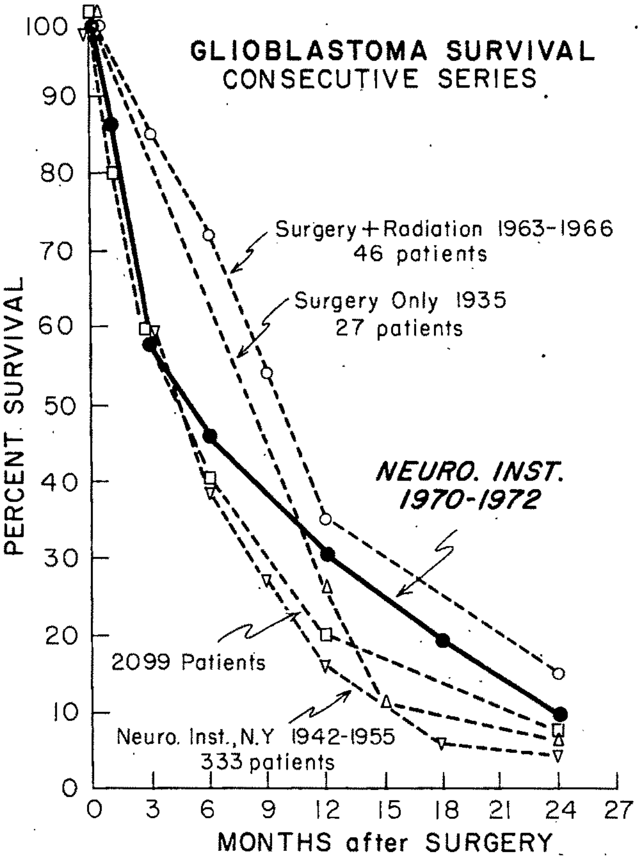

Fig 4.—All of these series are consecutively treated patients with glioblastoma. Surgery + Radiation 1963-1966[16]; Surgery Only 1935[13]; 2,099 patients[15]; Neuro. Inst., NY 1942-1955.[14]

trols are used for comparison. The very low 24-month survival rate (1 of 23) in those who actually received chemotherapy makes this objection unlikely.

Group B has a better internal subgroup control (nonchemotherapy) for evaluating the effect of chemotherapy on survival, than does group A. All patients in group B had primary glioblastoma when they entered the study and completed what many would consider optimal conventional treatment for glioblastoma: internal surgical decompression when motor and speech areas were not involved and a full course (6,000 rads using cobalt 60) of radiotherapy. Since all chemotherapy patients in group B lived for at least six weeks after initiation of nitrosourea chemotherapy, they must have lived long enough for some oncolytic effect of the chemotherapy to have occurred, if indeed there is such an effect in human glioblastoma. Survival of 50% of the patients for at least 12 months in the chemotherapy subgroup suggested a favorable trend, though not significant, when compared with nine months in the nonchemotherapy subgroup (Table 2). A limited amount of preselection may explain this trend in favor of chemotherapy. Two elderly patients with severe postoperative deficits were not given chemotherapy because of their poor prognosis, but they died shortly after completing a course of radiotherapy. This trend (in the 50% survival figures) was reversed by 24 months when only 5% of the chemotherapy subgroup were living, whereas 24% of the nonchemotherapy subgroup were still alive (Fig 2). The exclusive use of 24-month survival data could also introduce an apparent bias, because of the very few patients in the treated and untreated groups.

Great caution must be exercised in comparing group B patients with historical or concurrent controls. All group B patients were guaranteed at least seven weeks of survival from the time of initial surgery, because they were selected as those who had completed a full course of radiotherapy. They were usually guaranteed more than seven weeks of survival, because only patients who remained in relatively good clinical condition throughout the course of radiotherapy usually completed the full course. A falsely augmented 50% survival rate (12 months) would be apparent if group B chemotherapy patients were compared with group A nonchemotherapy patients (4.2 months) or with other consecutive series without chemotherapy (Fig 4, 5.5 to 11 months).

Group C patients, those who were prospectively randomized soon after surgery to receive either radiotherapy alone or radiotherapy plus chemotherapy, should theoretically provide the best internal controls for evaluating the benefits of chemotherapy. The trend toward an increase in 50% survival with chemotherapy, which was seen in groups A and B, was barely apparent in group C, reflecting the more equal matching of the chemotherapy and nonchemotherapy subgroups of group C (Table 1). The trend toward prolonged survival (25%) at 24 months in the nonchemotherapy subgroup as compared to the chemotherapy subgroup (6%) makes it very unlikely that chemotherapy, as given in this study, prolongs survival in human glioblastoma.

Many of the nonchemotherapy patients in groups A, B, and C received hyperbaric oxygen during radiotherapy in an effort to increase the tumor's radiosensitivity. Subsequent studies, however, from this Center show no prolongation of survival in glioblastoma patients who receive hyperbaric oxygen during radiotherapy.[4]

Duration of survival has been used as the major end point in this study, because it appears to be the most clearly defined, most frequently used, and most easily reproduced end point. It is a good but imperfect guide to an agent's oncolytic effect, because survival may be artificially prolonged by steroids or vigorous medical support. These were not used extensively during terminal illness in the present study.

Another way of estimating a treatment's oncolytic effect is to measure the progression-free interval. This is most easily done in patients who have survived surgery in good neurological condition. In these patients, the persistence of "good" quality of life would closely approximate the progression-free interval, assuming that non-tumor-related causes for deterioration are excluded. An evaluation of a treatment's effectiveness in prolonging good quality of survival is of utmost importance, because this is the ultimate aim of any medical or surgical intervention. In the present study, there was no prolongation of good quality of survival in patients treated with chemotherapy as compared with those who did not receive chemotherapy (groups B and C, Table 3).

Several factors have been implicated in other reports as being associated with a worse prognosis in patients with glioblastoma. These include old age, histological grade (4), a short duration of preoperative symptoms, a severe postoperative clinical deficit, a small surgical resection, or the absence of radiotherapy.[14,16-19] In the present study, only old age (greater than 64 years), severe postoperative neurological deficit, and the onset of symptoms less than 12 months prior to surgery correlated with a shorter survival (Table 4). A trend in favor of histologically less malignant tumors is suggested by the presence of grade 3 astrocytomas in all four patients who were living without clinical recurrence for more than 31 months after initial surgery. This study provides no information regarding the effect of radiotherapy on glioblastoma, because most good-risk patients were given postoperative radiotherapy.

The use of three different kinds of nitrosoureas represents a methodologic weakness in the evaluation of any one of these agents. The development, after the study was initiated, of agents that appeared more promising led to the changes in drug protocol. These changes were thought to be justified because of the apparent lack of benefit from the initial nitrosoureas.

Other studies suggest a beneficial effect of nitrosourea chemotherapy on patients with glioblastoma.[5-7,10,11] These have usually been uncontrolled studies on patients with recurrent brain tumors, some of which were glioblastomas. There are a few controlled studies of patients with primary glioblastomas who have been treated with adjuvant nitrosourea chemotherapy.[4,8,9] Preliminary findings have been reported after these patients have been followed up for less than one year. Median survival has been similar to that of group B patients in our study.

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The following were also members of the Brain Tumor Study Group: William Bauman, MD; James Brown, MD; Abe Chutorian, MD; Carl Feind, MD; Eugenia Gamboa, MD; Sadek Hilal, MD; John Kovach, MD; Edward Schlesinger, MD; Daniel Sciarra, MD; and I. Bernard Weinstein, MD.

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Extrajunctional Acetylcholine Receptors

Alterations in Human and Experimental Neuromuscular Diseases

Steven P. Ringel, MD; Adam N. Bender, MD; W. King Engel, MD

• Diffuse extrajunctional acetylcholine receptors (AChR) of skeletal muscle fibers were readily visualized by light and electron microscopy in muscle biopsy specimens of experimental denervation and human denervating diseases by use of an α-bungarotoxin immunoperoxidase technique. In peripheral neuropathies and various motor neuron diseases, a significant number of muscle fibers appearing denervated by histochemical criteria have diffuse extrajunctional AChR like those experimentally denervated by cutting the motor nerve supply. In portions of muscle fibers experimentally deprived of neuronal influence by direct injury, diffuse extrajunctional AChR developed, demonstrating that a denervation-like diffuse appearance of extrajunctional AChR can develop other than with neuronal damage, ie, it can be myogenous. Similar extrajunctional AChR was seen in some regenerating fibers of human myopathies, especially inflammatory myopathies.

***(Arch Neurol* 33:751-758, 1976)**

A new immunoperoxidase staining method[1] visualizes α-bungarotoxin (αBT), which binds specifically and relatively irreversibly to nicotinic acetylcholine receptors (AChR).[2] In normally innervated mature muscle fibers, the AChR molecules are confined to the neuromuscular junction.[1] In experimental denervation and in human denervating illnesses, extrajunctional AChR becomes evident along the entire muscle sarcolemma.[3,4] Recently, it has been proposed that there may be more or less subtle defects of motor influence on muscle fibers in certain neuromuscular diseases not generally considered neurogenic.[5,6] Accordingly, the muscle biopsy specimens of patients with various neuromuscular diseases have been studied with the αBT immunoperoxidase method in order to evaluate whether "denervation-like" change in the muscle fibers in the form of diffuse extrajunctional AChR was present.

In physiological studies,[7] extrajunctional AChR was evident in surviving nerve-free segments of muscle cut distal to the motor point (ie, the zone of the neuromuscular junctions). Animal experiments were conducted to further evaluate this possibility, because a denervation-like appearance of extrajunctional AChR theoretically might be expected to occur in any portion of a surviving muscle fiber deprived of neuronal influence on a "myopathic" basis.

MATERIALS AND METHODS

Human Muscle Biopsy Specimens

Fresh-frozen biopsy specimens from 173 patients with a variety of neuromuscular diseases were selected from those stored in liquid nitrogen. Ten-micron cryostat sections were placed in wells on Teflon-coated slides (three serial sections per slide). The usual cross-sectional area of the specimens was about 50 to 115 sq μm. Alpha-bungarotoxin (5×10^{-8}M) was applied in drops to the two lateral sections for 45 minutes at ambient temperature (20 C). The third (control) central one was incubated in buffer without αBT. The sections were fixed for 30 minutes at 4 C in a periodate-lysine-paraformaldehyde solution,[8] and then successively incubated for 45 minutes each at 20 C in rabbit antibody to αBT and peroxidase-conjugated goat antirabbit immunoglobulin. Postfixation for 30 minutes was performed with 2% glutaraldehyde in 0.1M sodium phosphate buffer at pH 7.4. Staining was with 3,3′-diaminobenzidine, 0.1 mg/ml, and hydrogen peroxide 0.001% in 0.05M tris-hydrochloric acid buffer at pH 7.6. The tissues were dehydrated in graded methanols, cleared in xylene, and mounted. Serial sections from each fresh-frozen muscle biopsy specimen were also stained with the modified trichrome, myo-

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fibrillar adenosine triphosphatase, nicotinamide adenine dinucleotide-tetrazolium reductase (NADH-TR), nonspecific esterase, and alkaline phosphatase reactions.[6,9-11]

Selected patients underwent motor point muscle biopsies[12] for electron-microscopical as well as light-microscopic examination. In the biopsied tissue, the neuromuscular junction zone was identified, selected, and trimmed[13] after prefixation for two hours at 4 C in 2% paraformaldehyde in 0.1M sodium phosphate buffer, pH 7.4. Teased whole muscle fibers were then treated with the same αBT, fixative, and staining solutions as detailed above, except that one-hour incubation times were used in αBT and each antibody solution. The stained fibers were osmicated in 1% OsO_4 in 0.1M phosphate buffer at pH 7.4 for one hour, dehydrated in graded methanols, and then embedded in either Epon 812 or low-viscosity Spurr. One- to five-micron sections were examined under light microscopy, and 70 nm sections under an electron microscope.

Experimental Animals

Denervation Study.—Either a sciatic or a phrenic nerve of 150- to 200-gm National Institutes of Health-strain rats was transected. Animals were killed at intervals over the next 2 to 45 days. The gastrocnemius and soleus muscles were used for frozen-sections for light-microscopical study. Teased diaphragm muscle fibers from zones rich in end-plates were examined by electron-microscopy. All tissue was handled as outlined above for human tissue. The nondenervated leg muscles or hemidiaphragms served as controls.

Freeze or Crush Injury.—A freeze injury 5 mm in diameter was induced in the right quadriceps of anesthetized rats using a liquid-nitrogen-filled metallic cylinder held for 60 seconds against the skin over the muscle. Crush injuries were performed on the quadriceps with a hemostat after exposure of the muscle through a skin incision. Animals were killed at 5, 10, and 15 days after the injuries and fresh-frozen cross-sections of the muscle were studied as discussed above. Quadriceps of the opposite legs served as controls.

To evaluate the effects of crush injury on a nerve-free segment of muscle, the sternohyoid muscle of rats was exposed. This muscle was about 15 mm long. The hypoglossal nerve was identified and a 1-mm-wide crush injury was performed on the muscle 2 mm distal to the motor point, as described by Hall-Craggs.[14] Additional animals underwent simultaneous hypoglossal nerve section and crush injury to the same muscle. All of these muscles and the contralateral control muscles were removed at various intervals from 1 to 17 days after injury and frozen. Longitudinal and cross sections were studied as described above.

Recording

Recording the number of αBT-positive fibers per biopsy is intended only to substantiate qualitative aspects of the pathogenic process in the various diseases, as in the experimental models. Precise quantitation is not appropriate because the muscle biopsy specimen is a random sample and not necessarily quantitatively representative of the patient's musculature.

RESULTS

Human Muscle Biopsies

Biopsy specimens of 25 patients with amyotrophic lateral sclerosis (ALS) or peripheral neuropathy contained muscle fibers considered by histochemical criteria to be denervated, ie, small fibers angular in cross-sectional contour that were stained darkly by nonspecific esterase and NADH-TR reactions (Fig 1, left). In 60% of these specimens, some of the denervated-appearing fibers also showed a distinct brown rim with the immunoperoxidase method, indicating the presence of extrajunctional receptor (Fig 1, right). In 64% of the ALS patients and 36% of the peripheral neuropathy patients, there were more than ten such fibers per biopsy specimen. On morphologically normal fibers no extrajunctional staining was seen; the only staining was at end-plates that corresponded to those seen on serial sections by nonspecific esterase staining. On the denervated-appearing fibers, the ultrastructural staining was considered to be rather even, without clearly accentuated regions of increased staining (allowing for minor irregularities in the 10-μ-thick sectioned fibers). The extrajunctional AChR staining was present on a variable and minor percentage of both type I and type II "histochemically denervated" fibers, the majority being unstained. Biopsy specimens having large numbers of small angular fibers in groups had up to about 50% of those fibers stained. In specimens with fewer small angular fibers scattered through the sample, only rare ones were stained, sometimes as few as one or two per specimen (Table). Target fibers in the denervation biopsy specimens were not stained.

Ultrastructurally, positive fibers showed αBT staining diffusely along the plasmalemma, as well as staining of the neuromuscular junction in a pattern identical to that in the normal human muscle[1,2] with predominant localization at the peaks of the postjunctional folds of the plasmalemma. In normal fibers, the nonjunctional plasmalemma was unstained at the ultrastructural level. ("Sarcolemma" is used to designate light-microscopy localizations, and "plasmalemma" for the more precisely defined electron-microscopy localizations.)

Of 11 patients with either infantile or juvenile proximal spinal muscular atrophy, all of the former and one third of the latter biopsy specimens showed more than ten fibers per sample, with faint extrajunctional AChR staining of small round fibers, in groups, but none in the large fibers. In all of the specimens many of the positive small fibers also showed small areas of darker staining on portions of the sarcolemma, in regions where neuromuscular junctions were absent on serial sections stained with the nonspecific-esterase reaction. It could not be determined whether these darker foci represented increased concentrations of AChR or minor tissue irregularities causing that appearance.

In 59% of 27 patients with inflammatory myopathy (polymyositis/dermatomyositis), diffuse extrajunctional AChR was seen in small round or roungulated (round-to-angular), presumably regenerating, fibers (Fig 2, left). These fibers were dark on modified trichrome staining and NADH-TR staining with a coarse granular network pattern (Fig 2, center and right), contained large vesicular nuclei with prominent nucleoli, and were morphologically quite distinct from the small, angular fibers that were positive in ALS and peripheral neuropathy.

In 46% of 11 patients with a limb girdle myopathic syndrome, with frankly myopathic biopsy specimens and brief-duration, small-amplitude,

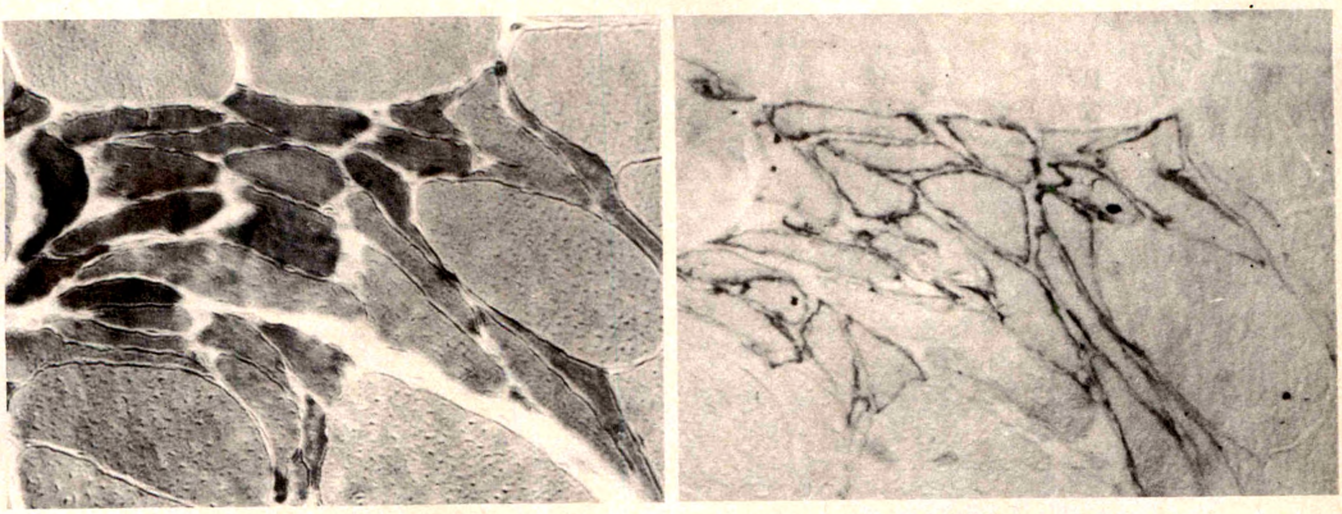

Fig 1.—Human muscle fibers, fresh-frozen, in serial cross-sections, from patient with lower motor neuron disease. Left, Group of small, dark, angular, presumably denervated fibers and normal-appearing, light-staining large rounded fibers (nonspecific esterase × 230). Right, Distinct dark α-bungarotoxin staining present on sarcolemmal membrane of angular fibers (no counterstain × 230).

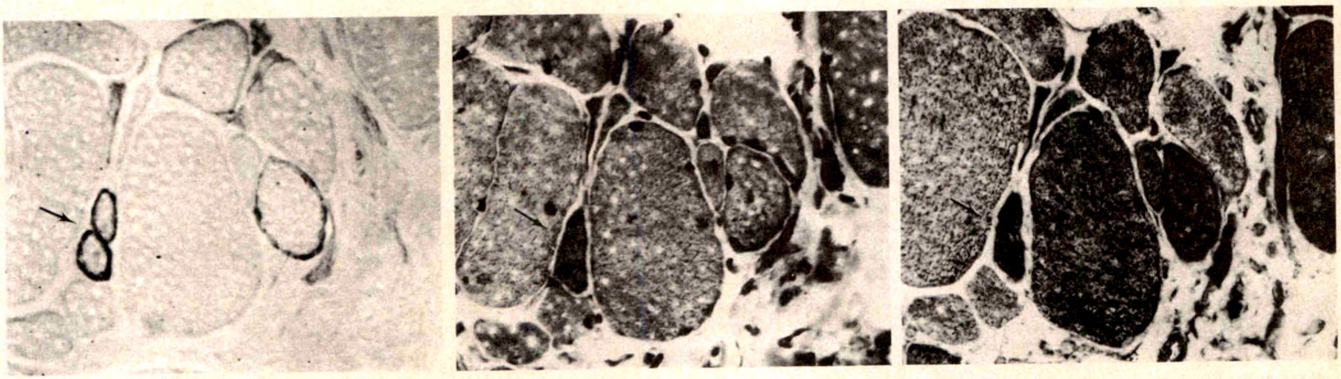

Fig 2.—Human muscle fibers, fresh-frozen in serial cross-sections, from patient with inflammatory myopathy (polymyositis). Left, Dark α-bungarotoxin staining present on sarcolemmal membrane of several small, round, regenerating fibers. One appearing undivided by careful microscopic examination in other sections is split in this section (arrow). Two very small angular fibers gave slight sarcolemmal staining (no counterstain × 400). Center, Small rounded, presumably regenerating fibers contain large, internal vesicular nuclei, and with other stains increased RNA activity. One is very darkly stained (arrow) (modified trichrome × 400). Right, Regenerating fibers are often dark with nicotinamide adenine dinucleotide-tetrazolium reductase (× 400).

overly abundant (for the degree of effort) motor unit action potentials by electromyography,[5] occasional scattered NADH-TR-dark, small angular and small round fibers with diffuse extrajunctional receptors were seen (Fig 3).

In some cases of rare disorders there were more than ten fibers per biopsy specimen with extrajunctional AChR staining (Table, group B). In some neuromuscular diseases, rare (< 10/biopsy specimen) scattered positive fibers were seen in some specimens (Table, group C). Biopsy specimens in a number of other conditions did not contain any αBT-positive fibers (Table 1, group D).

Experimental Animals

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Denervation Study.—After experimental denervation of rat muscle, changes in AChR distribution were seen as early as two to three days. An increase occurred in the amount of normally scant staining of the parajunctional sarcolemmal membrane within 10μ of the neuromuscular junction. From 3 to 14 days, there were, on cross-sections, enlarging zones of fibers with diffuse extrajunctional sarcolemmal AChR. The center of these zones usually contained a number of αBT-stained end-plates, suggesting that the pathological extrajunctional AChR was initially greater in the central region of the fiber near the neuromuscular junction. By 14 days, intense staining was uniformly present on the entire sarcolemma of all of both type I and type II fibers throughout the cross-section (Fig 4). Occasionally, staining was also located, by electron microscopy, on membranes of the initial portion of t-tubule membranes (which are contiguous with the plasmalemmal membrane) where they were entering the muscle fiber; this was usually in regions of most intense sarcolemmal staining. After three to four weeks, the light-microscopically evident extrajunctional AChR staining intensity progressively decreased, while the junctional region remained

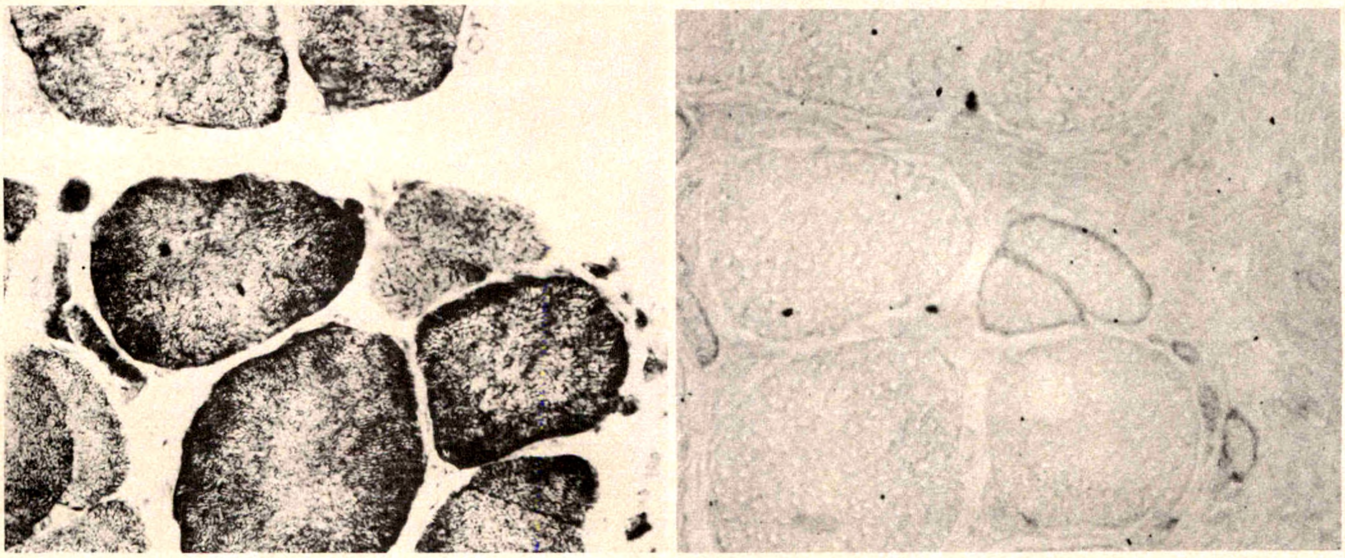


Fig 3.—Human muscle fibers, fresh-frozen in serial cross-sections, from patient with myopathic limb-girdle syndrome. Left, Large, medium-sized, and small fibers present; small ones are rounded and angulated (nicotinamide adenine dinucleotide-tetrazolium reductase ×300). Right, α-bungarotoxin staining of sarcolemmal membrane seen in two medium-sized roungulated fibers as well as in small rounded fibers (no counterstain ×300).

Fig 4.—Rat gastrocnemius muscle fibers, fresh-frozen cross-section, 14 days after denervation by section of sciatic nerve. Distinct dark sarcolemmal α-bungarotoxin staining is seen in all fibers. In addition, neuromuscular junction (end-plate) stains darkly (upper right) (no counterstain ×675).

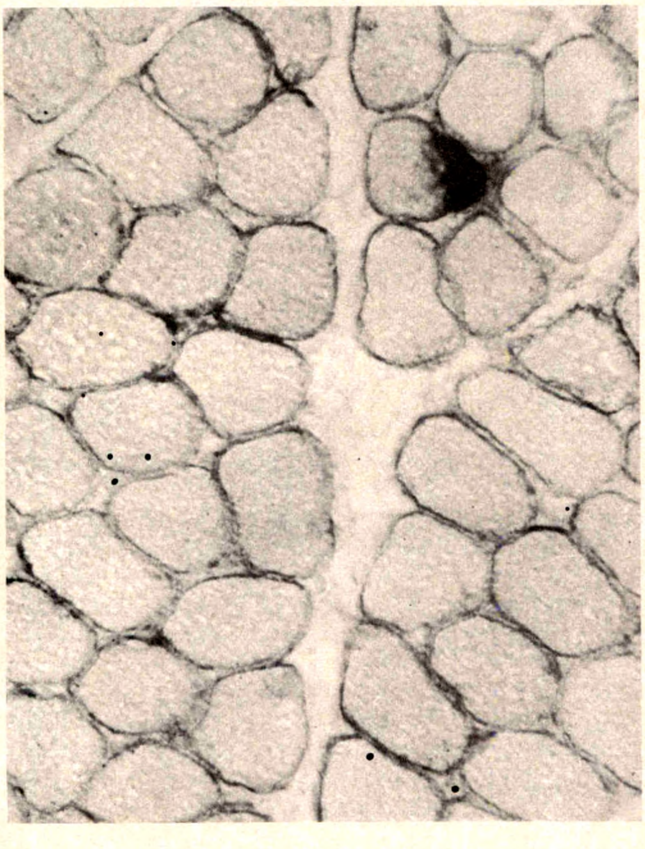
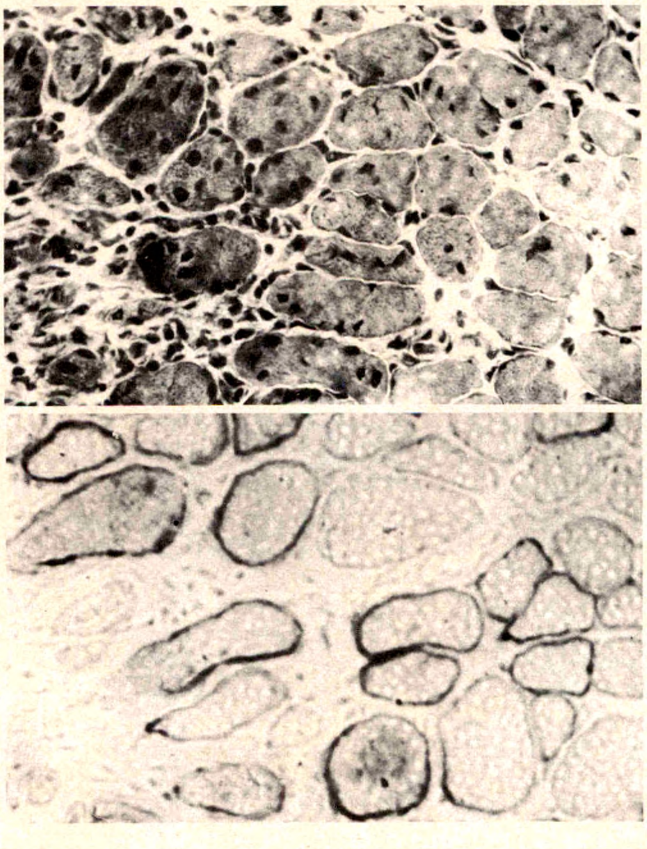


Fig 5.—Rat quadriceps muscle fibers, fresh-frozen cross-section, ten days after crush injury. Top, Intermediate zone between normal and necrotic zones contains regenerating fibers, identified by their small round appearance, large internal vesicular nuclei with prominent nucleoli, and dark staining (modified trichrome ×300). Bottom, Similar field shows that virtually all regenerating fibers contained diffuse sarcolemmal membrane α-bungarotoxin staining. (no counterstain ×300).



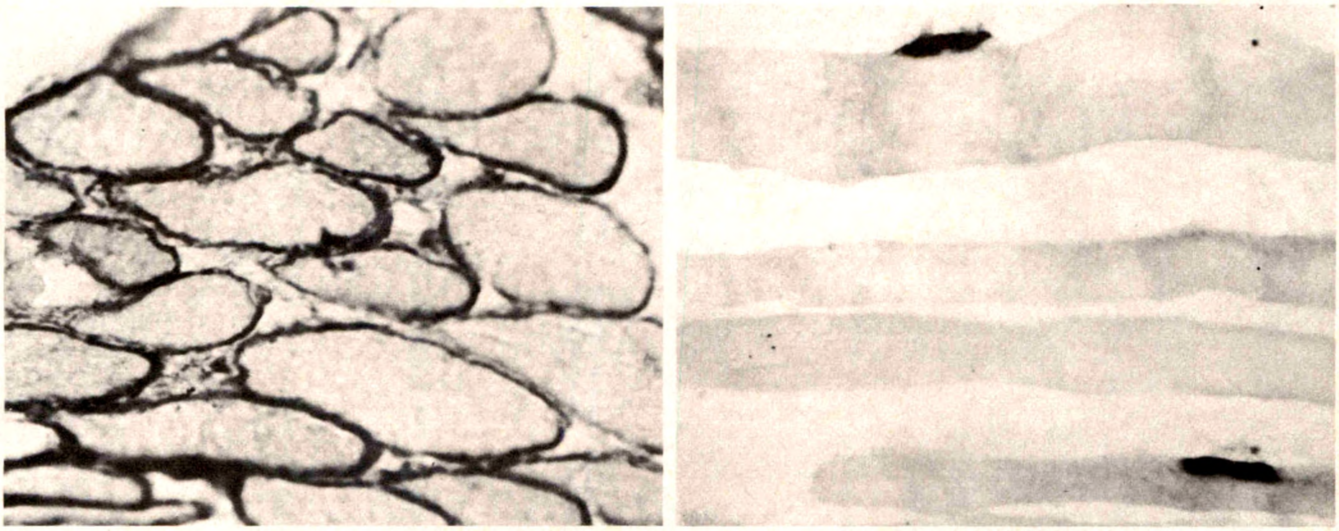


Fig 6.—Rat sternohyoid muscle fibers, fresh-frozen longitudinal-oblique sections, seven days after 1-mm crush was performed distal to end-plate region (α-bungarotoxin stain, no counterstain). Left, Distal to crush injury, where muscle fibers are morphologically intact and of normal diameter, diffuse extrajunctional sarcolemmal staining is present on all of them (×625). Right, Area proximal to crush shows staining at two neuromuscular junctions (end-plates) but no extrajunctional sarcolemmal staining (×600).

darkly stained. By six to eight weeks, almost no extrajunctional receptor staining could be seen by light microscopy.

Freeze or Crush Injury.—After either freeze or crush injury, regenerating muscle fibers were present in an intermediate zone between normal and necrotic zones. The regenerating fibers were identified by their small, rounded appearance, large vesicular nuclei with prominent nucleoli, and dark staining in fresh-frozen sections with the modified trichrome and NADH-TR reactions, the latter in a coarsened granular pattern (Fig 5, top). In cross-section, these regenerating fibers showed diffuse extrajunctional AChR staining (Fig 5, bottom).

After a 1-mm crush injury to the sternohyoid muscle 2 mm distal to the motor point, diffuse sarcolemmal AChR appeared in regenerating muscle fibers of the crush zone and in a narrow region immediately adjacent to it. Those fibers were thin, multinucleated muscle straps with vesicular nuclei and basophilic cytoplasm, presumably regenerative resulting from fusion of mononuclear myoblasts. Acetylcholine receptors also appeared in the sarcolemma throughout the entire distal nerve-free portions of all the muscle fibers (Fig 6, left). Those "recovering" segments of original fibers distal to the crush were of normal diameter and showed no (or in a few fibers sometimes only minimal) features of regeneration. They all had extrajunctional AChR throughout the sarcolemma as early as four days. No extrajunctional AChR was present in the proximal, innervated segment, and the end-plates of the proximal segment appeared to be normally stained with αBT (Fig 6, right). When the sternohyoid muscle was denervated as well as crushed, diffuse extrajunctional AChR appeared in both the proximal and distal segments to equal degree.

COMMENT

With the αBT-immunoperoxidase staining technique, human denervated muscle fibers are distinguished by the presence of diffuse extrajunctional AChR.[3,4] However, in ordinary denervation diseases, such as ALS and peripheral neuropathy, only some of the small angular fibers presumed to be undergoing denervation atrophy show diffuse extrajunctional AChR. The time course of development of, and subsequent loss of, extrajunctional staining in experimentally denervated rat muscle may explain this. Extrajunctional staining appears three to four days after experimental denervation, peaks in about two weeks, and begins to decrease at about three to four weeks. After six to eight weeks, extrajunctional AChR is no longer detectable on the denervated fibers by light microscopy, confirming earlier work with αBT-autoradiography.[15] If the time course in the human muscle fibers is similar, only those fibers denervated within a certain critical time period would have stainable extrajunctional AChR. Accordingly, the small angular fibers appearing denervated by histochemical criteria but lacking detectable extrajunctional AChR may have been denervated longer than that period of time.

In certain diseases, a possible explanation of failure of all the fibers that histochemically appear denervated to show diffuse extrajunctional receptor could be the presence of a serum factor blocking AChR. Such a factor has been shown in myasthenia gravis (MG).[16] That factor blocks the in vitro binding of αBT to both junctional and extrajunctional AChR. In MG patients, small angular muscle fibers with the histochemical characteristics of denervated fibers are often present,[17] but in the ten biopsy specimens studied no extrajunctional AChR was demonstrable, perhaps because there was accumulation of the blocking factor on extrajunctional receptors of those presumably denervated fibers.[18] This possibility is

Positive Fibers in Various Neuromuscular Disorders*

Disease	No. of Patients	Total Abnormal	No. of Abnormal Fibers		Normal
			0-10	>10	
Group A					
Amyotrophic lateral sclerosis	14	9	0	9A†	5
Peripheral neuropathy	11	6	2A	4A	5
Infantile spinal muscular atrophy	5	5	0	5R‡	0
Juvenile proximal spinal muscular atrophy	6	3	1R	2R	3
Polymyositis/dermatomyositis	27	16	7R	9R	11
Limb girdle myopathic syndrome	11	5	3R	2A,R	6
Group B					
Ragged-red fiber biopsy specimen,[29] various	11	1	0	1A	10
Oculocraniosomatic vacuolar myopathy neuropathy syndrome[32]	1	1	0	1A	0
Congenital morphologically nonspecific myopathy	5	2	0	2R	3
Rod disease, juvenile onset, atypical	1	1	0	1R	0
Atypical proximal-distal vacuolar myopathy-neuropathy syndrome	2	1	0	1R	1
Group C					
Duchenne muscular dystrophy	12	3	3R	0	9
Ischemia (amputated leg, peripheral vascular disease)	1	1	1R	0	0
Facioscapulohumeral syndromes	10	1	1R	0	9
Myotonic atrophy	8	1	1R	0	7
Type II fiber atrophy	4	1	1A	0	3
Group D					
Myasthenia gravis	10	0	0	0	10
Fascilitating myasthenic syndrome	1	0	0	0	1
Continuous muscle fiber activities	2	0	0	0	2
Type I fiber hypotrophy with central nuclei	5	0	0	0	5
Central core disease	3	0	0	0	3
Rod disease, congenital	3	0	0	0	3
Myotonia congenita	3	0	0	0	3
Paramyotonia congenita	2	0	0	0	2
Arthrogryposis syndrome (two neurogenic, one uncertain)	3	0	0	0	3
Phosphofructokinase, adult-onset acid maltase, and phosphorylase deficiencies	3	0	0	0	3
Myoglobinuria, idiopathic (quiescent phase)	2	0	0	0	2
Hypokalemic periodic paralysis	1	0	0	0	1
Focal loss of cross striations	1	0	0	0	1
Hyperthyroidism	1	0	0	0	1
End-stage biopsy specimen	4	0	0	0	4
Total	**173**	**57**	**20**	**37**	**116**

*Light microscopy.
†Angular.
‡Round.

supported by the finding of reduced or absent staining of neuromuscular junctions by the αBT method in muscle biopsy specimens of some patients with MG.[18]

In patients with either infantile or juvenile proximal spinal muscular atrophy, only the small, round fibers showed extrajunctional AChR. This was present on both alkaline phosphatase-negative (nonregenerating) and the few positive (regenerating) fibers.[11] Abnormally stained small fibers showed small areas of darker staining on portions of the sarcolemma in regions where neuromuscular junctions were absent in serial-sections stained with the nonspecific esterase reaction. These fibers thus were stained somewhat like some uninnervated animal muscle fibers in tissue culture, which have been reported by one group to show both faint diffuse staining over the sarcolemmal membrane and "hot spots" of more intense αBT binding spaced along the membrane.[19,20] In one preliminary electron-microscopy study of cultured muscle fibers, "hot spots" as a true phenomenon were suggested.[20] However, in our own electron-microscopic study of cultured chick, rat, and human muscle fibers, true "hot spots" were not found; larger foci of staining seemed more appropriately attributable to patchy obliquities of plasmalemma-sectioning or apparently random folds focally increasing membrane material.[21] In the biopsy specimens of infantile and juvenile spinal muscular atrophy patients, electron microscopy is required to determine whether there are true "hot spots" on fibers or simply minor tissue irregularities in the 10-μ sections causing that light-microscopical appearance.

Theoretically, a denervation-like change can occur in a muscle fiber not only with neuronal damage but also if a portion of the muscle fiber is deprived of neuronal trophic influence by a myogenous mechanism, eg: (1) blocking of "trophic-influence receptors" of the postsynaptic region of the neuromuscular junction, as might be occurring in MG[17]; (2) longitudinal splitting of part of the fiber away from the neuromuscular junction; (3) necrosis between a surviving part of the fiber and its neuromuscular junction; and (4) fibers regenerated from myoblasts not yet innervated in vivo or in tissue culture.[21-23] With either experimental freeze or crush injury to muscle, we were able to demonstrate diffuse extrajunctional receptor as early as four days in the regenerating original fibers. When the crush injury was applied distal to the neuromuscular junction, only in the distal nerve-free segment did "recovering" muscle fibers develop extrajunctional AChR (and they did so within four days), confirming earlier iontophoretic findings demonstrating the appearance of extrajunctional sensitivity to acetylcholine only in the segments of muscle fibers distal to crush-transection.[7] In our study, when the nerve was cut at the time of the crush injury, the proximal segments of muscle fibers also developed extrajunctional AChR. The freeze and crush studies demonstrate that both not-yet-innervated regenerating fibers and surviving parts of fibers separated from their neuromuscular junctions by a myogenic mechanism (necrosis in experimental crush) develop diffuse extrajunctional AChR.

Previously innervated and matured muscle fibers that have become noninnervated by any of the first three myopathic mechanisms mentioned above, but remain viable, theoretically have two potential fates: (1) healthy survival after reinnervation by a collateral sprout of a nearby intact axon, or (2) progressive atrophy with all the changes of shape and histochemistry that occur in fibers denervated in ordinary denervation diseases. In contrast to ordinary neurogenic noninnervation, these three would be "myopathic noninnervation" mechanisms, but the cytological result in those muscle fibers would be the same. Whether fibers regenerated from myoblasts can survive without innervation for a prolonged period of time in vivo is not known.

In the acute phase of polymyositis/dermatomyositis, it has previously been suggested, based on the presence of frequent spontaneous fibrillation and positive-sharp potentials on electromyogram (EMG), that the terminal intramuscular nerve fibers and axonal endings are affected in addition to the muscle fibers, ie, there is an intramuscular inflammatory "distal neuronitis" or "neuromyositis."[24] In the majority of the patients with inflammatory myopathy we studied, there were some fibers with extrajunctional AChR. Mostly, they appeared to be recovering or regenerating fibers. These fibers were identical to recovering and regenerating fibers in experimental crush injury, and presumably were having at least a transient period of "metabolic good health" but lacked innervation. In that state they would have been expected to spontaneously fibrillate, as do aneurally regenerating muscle fibers in tissue culture.[25,26] As the fiber recovers/regenerates and becomes fully influenced by motor innervation, the diffuse AChR would be expected to disappear, a change that conceivably might be paralleled by loss of spontaneous potentials on EMG. Long-term patients or ones recovered from inflammatory myopathy can show a different picture on EMG, with the presence of some large polyphasic potentials with increased duration.[27,28] These are considered to reflect increased muscle fiber number and spatial density of some motor units, on the basis of collateral sprouting and successful reinnervation of muscle fibers not originally in these units. This aggrandizement and densification of the motor unit could, theoretically, result from a purely myopathic mechanism in the form of reinnervation of regenerated/recovered muscle fibers, as well as from any possible concomitant neural involvement in the disease. In such patients we do sometimes see some degree of histochemically evident type-grouping in the muscle biopsy specimens.

To possibly explain the occasional cases of rare disorders with more than ten fibers per biopsy specimen showing extrajunctional AChR, one may consider the following points. In the ragged-red fiber syndromes, especially those with ophthalmoplegia[29] or myoclonus epilepsy,[30] and in the oculocraniosomatic neuromuscular disorder with vacuolar myopathy and neuropathy (sometimes called "oculopharyngeal dystrophy" by others[31]), where the positive fibers were of angular contour, a number of the patients have histochemical evidence of an element of what we have considered "ordinary denervation"[29,30] in the form of small angular fibers dark with NADH-TR and nonspecific esterase (although now the possibility, at least, of an aspect of "myogenous deinnervation" must be considered). In several patients, those with atypical proximal-distal vacuolar-myopathic-neuropathic syndrome, with the congenital morphologically nonspecific myopathy syndrome, and the patient with juvenile-onset (noncongenital) rod disease, there were a number of rounded-contour regenerating-degenerating fibers present to probably explain their rounded αBT-positive fibers.

In some other disorders, there were some biopsy specimens with rare αBT-positive fibers. In type II fiber atrophy, the rare angular fibers showing extrajunctional AChR staining in one biopsy specimen are not surprising in view of the possibly neurogenic mechanism raised in regard to at least some instances of type II fiber atrophy and the finding of occasional fibers with the histochemical features of ordinary denervated fibers in those type II fiber-atrophy biopsy specimens[5,32] (although alternately, a myogenous deinnervation mechanism conceivably could be considered[32]). The rare fibers in a few of the patients with Duchenne muscular dystrophy and in the patient with ordinary ischemic myopathy from peripheral vascular disease that showed extrajunctional AChR were rounded in cross-sectional contour and appeared to be regenerating, as did the similar positive fibers in the congenital morphologically nonspecific myopathy patients.

The patients whose limb girdle neuromuscular syndrome is considered to be on a myopathic basis are those lacking large or long motor-unit potentials electromyographically, and significant type-grouping of muscle fibers histochemically. The major feature in biopsy specimens is the constellation of small and large rounded fibers, increased endomysial connective tissue, and necrotic, phagocytosed, and regenerating fibers with none or only rare small NADH-TR-dark angular fibers. The regenerating fibers (or "regenerating-degenerating" fibers, designated when both features seem to be present in a fiber) typically are dark with NADH-TR, have a granular or increased-decreased pattern with that staining, and have a round cross-sectional contour.[33] Some of these small rounded fibers had extrajunctional AChR. In addition, there were occasional small NADH-TR-dark angular fibers with extrajunctional AChR, suggesting that in at least some of those patients a minor element of noninnervation-like change was present, on a neurogenic or myogenously deinnervated basis or both. These occasional "denervated-appearing" fibers, which can occur in limb girdle myopathy syndrome, dermatomyositis/polymyositis, Duchenne muscular dystrophy, and congenital morphologically nonspecific myopathy, and perhaps in any myopathy, conceivably could be explained by the myopathic noninnervation mechanisms mentioned above.

It has been proposed[5,6] that target fibers, central core disease, myotonic atrophy, myotonia congenita, type I hypotrophy with central nuclei, rod disease, and at least some cases of type II atrophy may, at least in part, be caused by more or less subtle partial defects in the lower motor neuron influence on muscle fibers, ie, by "dysinnervation." However, we were unable to demonstrate diffuse extrajunctional AChR with regularity in any of these conditions, and in most, all fibers in all biopsy specimens were negative. This negative evidence, while failing to support a neurogenic component to these diseases, does not exclude one. It only demonstrates that if there is a subtle defect in innervation it does not manifest itself with the formation and persistence of diffuse extrajunctional AChR, detectable by the technique used. However, it should be remembered that 45% and 35%, respectively, of the denervated-appearing biopsy specimens in our patients with peripheral neuropathy with ALS had no fibers with detectable extrajunctional AChR staining. Target fibers, common in ordinary denervation and only in that setting, were also negative with the αBT reaction. It is possible that (1) they are denervated muscle fibers in a stage of change beyond the time-window (approximately 2 to 45 days after experimental denervation) in which diffuse extrajunctional AChR is detectable by this technique; (2) they do have diffusely increased extrajunctional AChR but not above the threshold of detectability of the technique used; (3) they are caused by an alteration of neuronal influence on them, but one that is only partial and not concomitantly allowing extrajunctional AChR to appear; or (4) they reflect an altered state of reinnervation, an idea favored by M. Fardeau, MD (oral communication, 1974), in which extrajunctional AChR is not present. Similar explanations may be suggested for the lack of αBT staining of muscle fibers in other abovementioned conditions in which altered innervation has been proposed as possibly playing a significant pathogenic role.

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Thiamine Triphosphate Levels and Histopathology

Correlation in Leigh Disease

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• Thiamine and thiamine triphosphate (TTP) values were assayed in various brain regions in 11 controls and 13 patients with subacute necrotizing encephalomyelopathy (SNE, Leigh disease). The TTP values of normal brain were 5% of the total thiamine value. The relative TTP (or % TTP) level was consistently low in the pons, midbrain, and cerebellum of all the SNE brains. Twenty-five percent of the SNE brains had normal TTP levels in the frontal region. The TTP values correlated with the degrees of pathologic involvement in all sampled regions of the brain except the cerebellum. The concentration of thiamine in the mammillary bodies exceeded its concentration elsewhere in both control and SNE brains. The finding of low TTP levels in morphologically abnormal regions supports the hypothesis that TTP deficiency is etiologically related to SNE.

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Subacute necrotizing encephalomyelopathy (SNE, Leigh disease) is marked by extraordinary variability in clinical picture,[1-3] including the age at onset, rapidity of onset, the course of the disease, and the actual symptoms and signs. The urine of patients with SNE has been found to contain a nondialyzable substance that interferes with the formation or maintenance of thiamine triphosphate (TTP) in brain.[4-8] The occurrence of some false-positive results[7] and, more recently, false-negative results has raised doubts concerning the relation of the urine test to the pathogenesis of the disorder. Some have questioned whether SNE is a syndrome due to heterogeneous causes rather than a single genetic disease.[9]

For this reason attention has inevitably focused on the specificity of the preliminary finding that the proportion of TTP in the brains of affected children is reduced in SNE. If TTP deficiency is induced by a factor that prevents its formation or its maintenance in the brains of patients with SNE, then there should be a low proportion of TTP in such brains, particularly in those regions in which the lesions are maximally developed.

METHODS

Portions of the brains of 13 patients with SNE were analyzed for their TTP content. Five of these were receiving thiamine at the time of their deaths. Three of these patients died at the Yale-New Haven Hospital. Diagnosis rested on the presence of typical lesions in brain stem regions and sparing of the mammillary bodies. Most cases also involved other portions of the nervous system, such as the spinal cord, dentate nucleus, and basal ganglia. The material from all patients was frozen shortly after autopsy and stored at −20 C for periods of time varying from three weeks to one year before analysis.

Control brain material for biochemical analysis was obtained randomly during autopsies on adults and children who died with neurologic (five) and nonneurologic conditions (six). Six brain tumor samples removed at operation were analyzed for TTP.

In three patients with SNE, the brain was cut longitudinally. One half was analyzed pathologically and the other half biochemically to compare the regional severity of pathologic changes with the symmetrical percentage of total thiamine as TTP. In the other nine patients, only selected portions of frozen, unfixed brain were analyzed. In two of these nine, the postmortem examinations were performed by one of us (G.B.S.); diagnosis in the remainder was established by neuropathologists in other institutions, though we reviewed the slides in three of these and a fourth was published.[10]

Thiamine and its phosphate esters were separated in deproteinized brain extract by electrophoresis,[11] paper chromatography,[12] and column chromatography. All three methods of separation gave comparable results. Column chromatography was the most convenient for analyzing large

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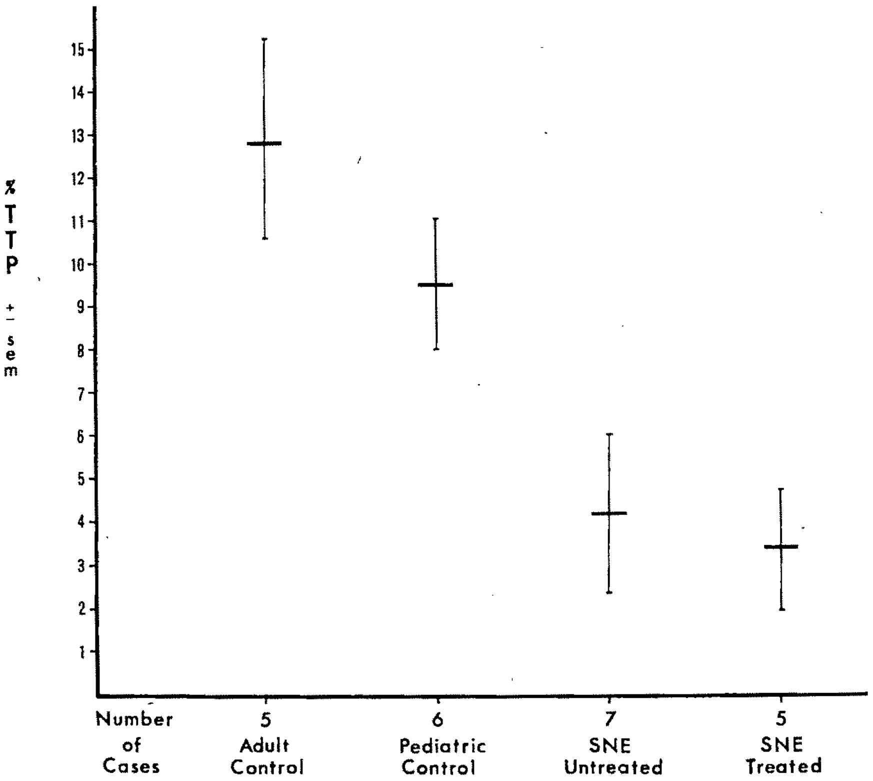
amounts of tissue; recovery was 85% to 96%. For chromatography, 1 ml of deproteinized brain extract was placed on a 5 × 50-mm column of AG 1 × 4, 200 to 400 mesh in the acetate form. Thiamine and thiamine monophosphate were eluted with 5 ml of H_2O, thiamine pyrophosphate with 5 ml of 0.125M (pH 5.0) sodium acetate buffer, and TTP with 5 ml of 1.0M (pH 5.0) sodium acetate buffer. Each fraction was freeze-dried and assayed for thiamine by the alkaline ferricyanide method.[11]

RESULTS

Total thiamine and TTP content were assayed in cerebrum (including cortex and basal ganglia), cerebellum, and various brain stem regions in 11 controls (five adults and six children), of whom four children and one adult had neurologic abnormalities. These included microcephaly, central nervous system leukemia, ventricular hemorrhage, trisomy 21, and herpes simplex encephalitis. The average total thiamine value in adults was 2.22μg/gm of wet weight (Table 1), three times the average total thiamine value in children, 0.69μg/gm. Despite this variation in total concentration, the percentage of thiamine as TTP was similar in the two control groups, being 11.4% in adults and 10.6% in children.

The TTP values showed no consistent regional variation in the control brains. In 19 determinations from the 11 controls, the mean percentage of TTP was 10.8% ± 3.9 SD (range, 5.3% to 17.0%). Thus, TTP values below 5% can be regarded as low (Figure). The TTP values in six brain tumors were in the normal range despite low total thiamine values (Table 2).

Despite the constancy of the relative TTP (%TTP) in control material, absolute amounts of TTP expressed as micrograms per gram of wet weight varied by two orders of magnitude. One control specimen from the frontal cortex of a 4-year-old battered child had a total thiamine value of only 0.06μg/gm and TTP value of 0.0052μg/gm. This absolute value is lower than that of some cases of SNE; yet, the relative TTP value is normal, 8.7%. Necrotizing lesions were not found in the cortex of this child at autopsy. The implication is that TTP may be biochemically less important



Relative thiamine triphosphate (TTP) values in frontal cortex. Difference between adult and pediatric controls not significant; difference between treated and untreated patients with subacute necrotizing encephalomyelopathy (SNE) not significant; difference between control and SNE groups combined significant (.005 < P > .0005).

Table 1.—Comparison of Brain Thiamine and TTP* Levels in Controls and Patients With SNE†

	No. of Patients	No. of Samples	Total Thiamine, μg/gm ± SD	TTP, % Thiamine ± SD
Controls, adult	5	10	2.22 ± 1.46	11.4 ± 4.2 (range, 6.7-17.0)
Controls, pediatric	6	9	0.69 ± 0.49	10.6 ± 3.6 (range, 5.3-16.8)
With SNE, untreated	8	10	0.57 ± 0.46	2.6 ± 4.4 (range, 0-13.2)
With SNE, treated	5	19	4.38 ± 2.54	2.0 ± 2.9 (range, 0-10.5)

*Thiamine triphosphate.
†Subacute necrotizing encephalomyelopathy.

Table 2.—Thiamine and TTP* Content of Brain Tumors†

Tumor	Thiamine, μg/gm	TPP, % Thiamine
Astrocytoma	1.23	8.7
Astrocytoma-oligodendroglioma	0.62	10.5
Glioblastoma multiforme	0.30	10.4
Hemangioblastoma	0.54	10.8
Meningioma	1.27	8.6
Meningeal sarcoma	0.29	11.6
Mean ± SD	0.71 ± 0.44	10.1 ± 1.2

*Thiamine triphosphate.
†None of these patients had received chemotherapy or radiotherapy.

in absolute amounts than in relation to other thiamine esters. For this reason, TTP is expressed as a percent of the total thiamine value.

Biochemical analysis was performed on 13 patients with SNE, five of whom had been treated with thiamine. Average total thiamine concentration in untreated patients was 0.57μg/gm, a figure not different from pediatric controls. Treated patients had average total thiamine values of 4.38μg/gm, roughly ten times higher. Relative TTP values were low ($< 5\%$), however, in both treated and untreated SNE groups ($P < .0005$), and treatment did not seem to have affected this (Figure, Table 1).

Unlike control brains, the brains of children who died of SNE demonstrated regional differences in TTP values (Tables 3 through 5). The cerebral cortex, with its underlying white matter, contained the highest levels of TTP. Of the 12 patients analyzed, three had normal cortical TTP values. In five patients, TTP values were between 1% and 5%, and only four had less than 1% of total thiamine value as TTP, three of which had no detectable TTP.

In the pons and midbrain, where lesions are most extensive in SNE, TTP values were uniformly low, varying from 0 to 3.3% in nine samples from four patients. In the spinal cord, where lesions occur often but not always, two specimens of cervical cord had values of TTP of 1% or less. A spinal cord specimen from a third patient had a normal proportion of TTP. In all three patients, there was extensive involvement of the upper spinal cord, but the third case was associated with no lesions in the thoracic cord. It is not clear if the specimen analyzed biochemically in this case was from a normal or abnormal region of the spinal cord.

In the cerebellar cortex and white matter, which usually contain few lesions, five of six patients had no detectable TTP, and the other had a value of 1.6%. Morphologic and biochemical changes are compared in the three cases studied in detail in Table 5.

Total thiamine values in control and SNE brains varied little from region to region except for the mammillary bodies, which contained several times more thiamine than other regions (Table 6). The brain thiamine levels of patients with SNE were elevated by treatment with thiamine derivatives, especially in the mammillary bodies where a level of 30μg/gm of wet tissue was recorded in one case. In only one instance was there enough material to determine the TTP content of the mammillary bodies in a case of SNE. It was 13% of the total thiamine. In two controls, the mammillary body TTP values were 16% and 17%.

Table 3.—Regional Thiamine and TTP* Content

	N	Thiamine, μg/gm ± SD	TTP,% Thiamine ± SD
		Untreated Cases of SNE† (8 Patients)	
Cortex	7	0.60 ± 0.57	3.97 ± 4.92
Cerebellum	2	0.47 ± 0.07	0
Pons	1	0.61	0
		Treated Cases of SNE (5 Patients)	
Cortex	5	3.14 ± 2.53	3.4 ± 3.1
Corpus striatum	2	3.01 ± 0.24	2.7 ± 2.7
Cerebellum	4	4.63 ± 3.53	0.4 ± 0.8
Dentate nucleus	1	2.93	1.4
Midbrain	2	5.10 ± .62	1.0 ± 0
Pons	3	2.96 ± .73	0.7 ± .8
Medulla	3	3.99 ± 2.66	2.4 ± .9
Cord	3	7.43 ± 1.01	4.2 ± 5.5

*Thiamine triphosphate.
†Subacute necrotizing encephalomyelopathy.

Table 4.—Incidence of Low TTP* Values in SNE† (13 Cases)

	Normal (>5%)	Low (<5%)	Absent
Cerebral cortex	3/12	9/12	3/12
Corpus striatum	1/2	1/2	0/2
Cerebellum	0/6	6/6	5/6
Brain stem	0/9	9/9	2/9
Cord	1/3	2/3	0/3

*Thiamine triphosphate.
†Subacute necrotizing encephalomyelopathy.

COMMENT

The consistent reduction in the relative TTP concentration in the brain stem correlated well with the regularity with which lesions were encountered in that region. The lesser consistency with which reduction in TTP concentration was encountered in spinal cord, basal ganglia, and cerebral cortex also correlated with a less common involvement of these regions pathologically. The least sensitive region with regard to pathologic changes was the frontal cortex where TTP values were normal in three of the 12 cases tested.

The only distinct exception to this pathologic and biochemical parallelism was the cerebellar cortex and white matter; this portion of the cerebellum in SNE patients consistently showed deficiencies in TTP values despite the rarity of lesions in that region.

Thus, there appeared to be a rough correlation in the brain of patients with SNE between the presence of lesions and the reduction in levels of TTP. To our knowledge, normal levels of TTP have never been described in the pons, midbrain, or cerebellum in any case of SNE. Normal levels of TTP were encountered in frontal cortex in only 25% of the cases of SNE.

Could the relative lack of TTP in the brains of SNE patients be an epiphenomenon, the result, perhaps, of a demyelinating lesion rather than the cause of one? The absence of TTP in morphologically unaffected regions of SNE brains argues against this. The presence of high or normal total thiamine values in treated and untreated children with SNE, even in regions that were morphologically affected by the disease, confers some degree of specificity to the finding of low TTP levels. Also, the presence of TTP in normal proportions in the largely unmyelinated brain of premature and neonatal controls suggests that a lack of myelin and a reduced proportion of TTP are not obligatory concomitants. Ideally, the brains of patients who died of demyelinating diseases in childhood should be examined, but such material has been unobtainable to date.

Table 5.—Detailed Correlation of Severity of Pathologic Changes With Thiamine and TTP* in Treated Cases of SNE†

Patient/Age, yr	Brain Region	Thiamine, µg/gm	TTP, % Thiamine	Pathological Finding‡
1/2	Cortex	1.58	8.3	0
	Lenticular nucleus	2.76	5.4	0
	Cerebellum	4.66	0.0	+2
	Midbrain	...	...	+4
	Pons	2.13	0.0	+4
	Cord	6.66	1.1	+3
2/2	Cortex	0.84	2.6	+1
	Lenticular nucleus	...	...	+1
	Cerebellum	2.49	1.6	0
	Midbrain	3.48	1.0	+1
	Pons	3.27	1.5	+1
	Cord	8.57	1.0	...
3/3	Cortex	2.92	0.7	0
	Lenticular nucleus	3.25	0.0	+2
	Cerebellum	1.78	0.0	0
	Midbrain	6.72	1.0	+3
	Pons	3.49	0.6	+2
	Cord	7.06	10.5	0 to +3

*Thiamine triphosphate.

†Subacute necrotizing encephalomyelopathy.

‡0 = normal; +1 = isolated focal necrosis; +2 = more generalized changes, but most of sample unaffected; +3 = most of sample affected; +4 = all portions of section involved.

Table 6.—Thiamine Content of Mammillary Bodies and Other Areas

Diagnosis	Patient Age,	Brain Sample	Total Thiamine, µg/gm Wet Weight
Trisomy 21	1 mo	Cortex	0.77
		Cerebellum	0.71
		Pons	1.84
		Mammillary body	7.88
Pneumonia	53 yr	Cortex	1.85
		Cerebellum	1.63
		Pons	0.91
		Mammillary body	7.10
Cardiac infarct	67 yr	Cortex	2.74
		Cerebellum	1.91
		Pons	2.18
		Mammillary body	6.65
SNE*†	2 yr	Cortex	1.58
		Cerebellum	4.66
		Pons	2.13
		Mammillary body	30.32
SNE†	3 yr	Cortex	2.92
		Cerebellum	1.78
		Pons	3.49
		Mammillary body	4.77

*Subacute necrotizing encephalomyelopathy.

†Treated with thiamine propyldisulfide and thiamine tetrahydrofurfuryl disulfide.

Subacute necrotizing encephalomyelopathy is transmitted as an autosomal recessive trait, and its clinical variability is encountered even within single families in which more than one child is affected.[3] For this reason, antemortem diagnosis has been difficult to establish. Either the stepwise deterioration or the autopsy diagnosis of SNE in a sibling has alerted clinicians to the correct diagnosis.

The pathologic signs of SNE also can vary, although typically the brain stem demonstrates symmetrical necrotizing lesions. The pontine tegmentum is involved in 92% of patients, the medullary tegmentum in 82%, the spinal cord is involved in 74%, and some of the basal ganglia in 67%.[2,3] The cerebral and cerebellar cortex are seldom involved. In contrast to Wernicke encephalopathy, which SNE resembles morphologically, the mammillary bodies in SNE are almost always spared.[2,3] One case has been reported without lesions in the brain stem, but with typical lesions in the spinal cord and basal ganglia.[13] Bargeton-Farkas and co-workers[14] reported a patient with only minimal, nonspecific brain stem changes in contrast to a sibling who had typical lesions both in kind and distribution. Hemorrhage may be seen in acute lesions, and cavitation in chronic ones. While the diagnosis in typical cases is easy, the full extent of morphologic variability in this condition is undefined.

One of the more promising aspects of early investigations into the cause of the condition was the possibility that the urine test might provide a secure antemortem diagnosis; however, a 6% false-positive rate has occurred (12 false-positive findings in 214 patients known not to have SNE as of January 1976). Between August 1968 and January 1976, a total of 29 patients whose urine was studied have been shown to have SNE by autopsy. The diagnosis in these was finally established by an autopsy in the patient (20 patients) or in a sibling (nine). The urine of six of these patients did not contain the interfering substance. Since the incidence of true positive results was greater ($\chi^2 = 112.5$, $P < .001$) than the incidence of false positive findings, the results of urine testing have supported the theory of an endogenous substance that inhibits the formation or maintenance or both of brain TTP in SNE and causes the disease.

The clinical and pathologic variability of SNE have led some to propose that SNE is more a syndrome than a disease. Since great clinical variability occurs even among affected members of the same family,[3] this is hardly a strong argument.

The existence of heterogeneous metabolic disturbances that can give rise to SNE was suggested by Hommes et al,[9] who described a deficiency in pyruvate carboxylase in the liver of affected children; however, this has now been found to be a secondary change in several patients in whom it first developed after the disease had run all or nearly all its course.[15] No abnormality in this enzyme has been found in at least two other patients with proved SNE (written communication from M. Utter, PhD, August 1975). Technical difficulties in assaying pyruvate decarboxylase, such as postmortem changes and inactivation during freezing, also make the initial findings difficult to interpret.[16] In only one case[17] was the finding of pyruvate carboxylase deficiency in the liver of a child with SNE established in a manner that excluded the possibility of an artifact. Thus, the issue of specificity has, to some degree at least, enveloped every aspect of this disease that concerns diagnosis and causation.

Thiamine triphosphage appears ubiquitously in all tissues that contain thiamine. It is present in the partially (or incompletely) myelinated brain of a premature infant and in a variety of brain tumors, as well as within kidney, liver, and heart.[18] It appears to be stable and does not deteriorate even after frozen tissue has been stored for many months. During the course of time in the freezer, thiamine pyrophosphate is hydrolyzed to free thiamine, but TTP is maintained absolutely and in relation to total thiamine (unpublished data).

Several attempts to create a TTP deficiency state experimentally have been unsuccessful. These have included (1) dietary thiamine deficiency,[19] (2) challenge of deficient animals with intraperitoneally administered high doses of glucose, and (3) administration of plasmocide, a substance that causes necrotizing brain stem lesions[20] (unpublished data). In a sense, our failure to produce, by a variety of techniques, a brain deficient in TTP argues in favor of the specificity of TTP loss in this disease, as some of these techniques cause lesions similar to those seen in SNE.

The reduction of TTP in SNE may be the result of the action of a nondialyzable substance that has been found in the urine, blood, and spinal fluid of these patients and their relatives. This substance may depress the synthesis or increase the destruction of TTP in brain. No direct evidence is available to establish this, but it is a reasonable hypothesis. The identity of this substance and the role of TTP in normal cerebral functioning are still unknown.

A curious difference between Wernicke encephalopathy and SNE is the less widespread distribution of lesions in Wernicke disease. Despite this, the mammillary bodies are almost always involved in Wernicke encephalopathy and almost never in SNE.

The high thiamine and TTP levels demonstrated in the mammillary bodies of normal and thiamine-treated individuals with SNE as compared to levels in other brain regions suggests that this tissue may be outside the blood brain barrier or at least have different transferases in its capillary network. We are unaware of anatomic support for this postulate. If true, however, it might be argued that the mammillary bodies could more easily be depleted of thiamine in deficiency states, resulting in the typical lesions of the classical thiamine deficiency disease.

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Fluorometric Determination of Pyruvate and α-Ketoglutarate in Cerebrospinal Fluid and Plasma of Infants and Children

A Simple Test That Screens for Metabolic Disorders

Jean Holowach Thurston, MD; Richard E. Hauhart; Jo Louise Seltzer, PhD; David B. McDougal, Jr, MD

• Levels of pyruvate and α-ketoglutarate in the cerebrospinal fluid (CSF) of 26 children, aged 4 months to 5½ years, with febrile seizures and of 19 children, aged 4 months to 14 years, with the diagnosis of epilepsy were not different from values seen in 119 "normal" children 8 days to 14 years of age. The CSF samples from 24 adults, 24 to 81 years of age, suspected of having a herniated disk were also examined. In the pediatric age group, the data showed a highly significant downward trend of CSF and plasma α-ketoglutarate values with age; pyruvate values did not change.

A correlation of the values of the two keto acids in the blood and CSF of 42 other children without apparent neurologic disease was also made. Findings in a child with thiamine deficiency suggest that CSF α-ketoglutarate may be a more sensitive indicator of deficiency than plasma α-ketoglutarate or pyruvate.

Measurements of these keto acids in plasma and CSF may be diagnostically useful in a variety of metabolic disorders. Findings in 155 children from birth (20 minutes) to 17 years of age without neurologic disease are submitted as a standard of reference.

(*Arch Neurol* 33:764-768, 1976)

This is a report of pyruvate and α-ketoglutarate concentrations in the cerebrospinal fluid (CSF) of infants and children. The study was stimulated by our interest in the pathophysiology of neurologic dysfunction in thiamine deficiency. In the brains of young thiamine-deficient mice, reduced activity of pyruvate and α-ketoglutarate dehydrogenase enzymes was reflected in a fourfold increase in brain pyruvate concentration and a sevenfold increase in α-ketoglutarate.[1] Although levels of pyruvate and α-ketoglutarate were also elevated in the plasma of these animals, the increases were relatively small, 50% and 40%, respectively, (only one tenth or less of the increases found in the brain). If such cerebral metabolite changes occur in human thiamine deficiency, they might be more accurately reflected in CSF than plasma. Therefore, standard fluorometric procedures were adapted for measuring the two keto acids in CSF (and plasma). The measurements proved useful in one child with progressive neurologic dysfunction associated with thiamine deficiency. Pyruvate measurements may also be of value in the study of hereditary enzymatic defects of pyruvate metabolism.[2-7] Clinical syndromes associated with the isolated defects of α-ketoglutarate metabolism have not yet been identified.

SUBJECTS AND METHODS

Selection of Patients

Aliquots of consecutive samples of CSF brought to the laboratory of St Louis Children's Hospital after lumbar puncture were promptly frozen at −20 C. The hospital records of all the patients with normal CSF findings—cell count, glucose and protein concentrations, and negative cultures for bacteria—were then reviewed. When there was no clinical indication of CNS disease, the patients were considered "normal" and were included in the study. One hundred nineteen cases fulfilled these criteria. Most of the CSF samples were from children with upper respiratory tract infections and otitis media; others were from children with gastroenteritis and with fever of undetermined cause. In these cases, lumbar puncture was performed to rule out the possibility of meningitis. Pyruvate and α-ketoglutarate levels in the CSF of 26 children with febrile seizures, 19 with chronic epilepsy, and 24 adults with the diagnosis of "possible herniated lumbar disk" were also measured. In addition, a correlation of the concentrations of the two keto acids in the blood and CSF of 42 other children was made.

Preparation of Extracts

CSF.—First, 0.5 ml of CSF was deproteinized with 0.1 ml of 3M $HClO_4$ in 4-ml plastic tubes. After mixing, the tubes were centrifuged at 10,000 rpm for ten minutes. Then, 0.5 ml of the supernatant fluid was neutralized with 180μl of 2M $KHCO_3$ in 3-ml Pyrex tubes. After effervescence had ceased, the tubes were centrifuged at 3,000 rpm for five minutes. The supernatant fluid was stored at −80 C until the time of assay.

Plasma.—First, 0.2 ml of plasma (or serum) was deproteinized with 0.035 ml of 3M $HClO_4$. After centrifugation (10,000 rpm for ten minutes) 0.15 to 0.17 ml of the supernatant fluid was neutralized with 0.07 ml of 2M $KHCO_3$.

Stability of Metabolites

CSF.—Three samples were kept at room temperature after lumbar puncture. Values for pyruvate and α-ketoglutarate in aliquots extracted and assayed one and two hours after collection did not differ from those seen in aliquots extracted and assayed immediately after collection of fluid. Pyruvate concentration fell 50% to 70% after being left overnight at room temperature.

No differences were found between pyruvate and α-ketoglutarate levels in three samples of CSF extracted and assayed immediately after lumbar puncture and in aliquots of the same samples

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extracted and assayed after three days at −20 C.

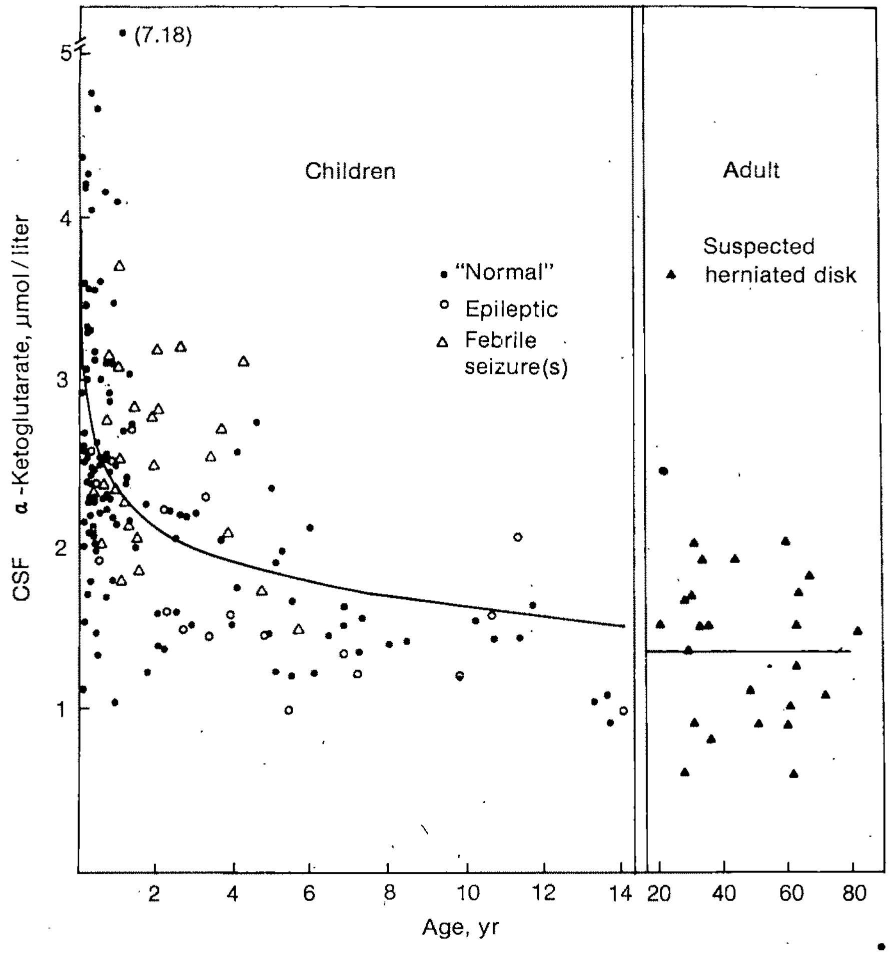
In six other samples of freshly collected and perchlorate-treated CSF, pyruvate and α-ketoglutarate levels were assayed prior to freezing at −80 C. At weekly intervals, the extracts were thawed, assayed, and then refrozen at −80 C. α-Ketoglutarate levels were unchanged after four weeks. Pyruvate levels were not significantly changed after storage at −80 C for three months. However, these extracts were much less stable when kept at −50 C. Since very low temperature freezers may not be generally available, it is recommended that CSF be extracted within two hours of collection, stored at −20 C to −80 C, and assayed within one week after freezing.

Levels of Pyruvate and α-Ketoglutarate in Cerebrospinal Fluid of "Normal" Children, Children With Seizures, and Adults With Suspected Herniated Disks

Diagnosis	Mean Age, yr (Range)	Pyruvate, μmol/liter		α-Ketoglutarate, μmol/liter	
		Mean ± SEM	Range	Mean ± SEM	Range
"Normal" (N = 119)	2.3 (8 days-14 yr)	126 ± 4	32-230	2.42 ± 0.09	0.9-7.2
Febrile seizures (N = 26)	2.0 (4 mo-5.5 yr)	124 ± 6	31-185	2.57 ± 0.12	1.5-4
Epilepsy (N = 19)	5.3 (4 mo-14 yr)	98 ± 6*	42-143	1.75 ± 0.12*	1-2.7
Herniated disk (N = 24)	47 (24 yr-81 yr)	103 ± 8†	40-251	1.37 ± 0.09*	0.6-2.2

*Differs from "normal" at $P < .001$.
†Differs from "normal" at $P = .011$.

Fig 1.—Cerebrospinal fluid (CSF) α-ketoglutarate levels as a function of age. When CSF α-ketoglutarate values for the children ("normal," epileptic, and those with febrile seizures) were plotted against $\log_{10}$ age (in years), there was a significant downward trend, $r = -0.5361$, $P < .001$ ($\alpha\text{-ketoglutarate}_{CSF} = -0.7668 \log \text{age [in years]} + 2.375$). No significant trend with age was seen in adult population. Line represents mean value.



Plasma.—No differences in pyruvate and α-ketoglutarate levels were found between plasma samples extracted and assayed immediately after collection and samples kept at room temperature for two hours before extraction. There was, however, a 20% to 30% drop in concentration of both keto acids when unextracted samples were left overnight at room temperature. Unextracted plasma samples stored for five days at −20 C showed no loss of pyruvate or α-ketoglutarate. Extracted plasma samples were stable for at least one month at −80 C.

Assay Methods for Metabolites

Metabolites were measured at room temperature in a fluorometer by a minor modification of the enzymic methods of Lowry and Passonneau.[5] In the α-ketoglutarate assay, glutamic dehydrogenase was increased from 5μg to 30μg/ml. Both reactions were carried out in 1 ml of reagent. The volume of plasma and CSF extracts used for pyruvate measurements was 3.5μl. For α-ketoglutarate assay, 50μl of plasma extract and 170μl of CSF extract were used. Standards and blanks contained a neutralized perchlorate solution equal in volume and concentration to that of the plasma or CSF sample used. The tubes were read prior to the addition of the enzyme and again when the enzyme reaction was complete. Addition of plasma and CSF extracts to pyruvate and α-ketoglutarate standards gave additive results.

In the α-ketoglutarate assay, the sensitivity of the fluorometer was set so that the full range of the galvanometer scale was equivalent to 10×10^{-7}M nicotinamide adenine dinucleotide, reduced (NADH). With the mean CSF value of α-ketoglutarate (2.5μmol/liter), the decrease in fluorescence due to the α-ketoglutarate in 170μl of extract was equivalent to 2.5×10^{-7}M NADH. Since α-ketoglutarate levels in CSF may be one half this concentration or less, proportionately more extract is required for an equivalent fall in NADH levels. With an unknown α-ketoglutarate concentration in spinal fluid and a limited quantity of extract, it is recommended that the α-ketoglutarate determinations be run as single repeat assays. After this measurement, the volume of CSF needed can be determined. Repeat single assays for α-ketoglutarate levels were reproducible to 5%.

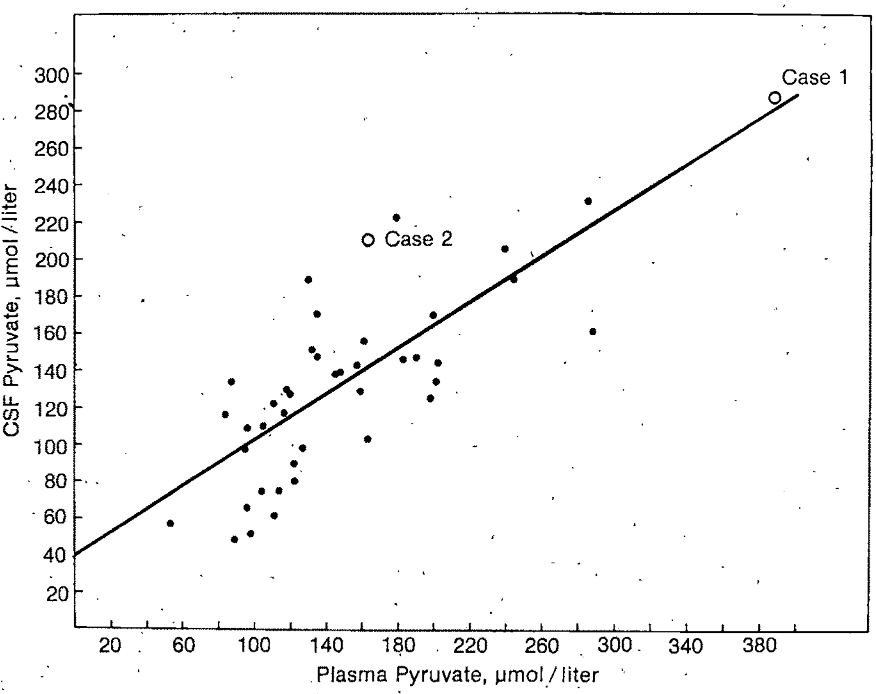
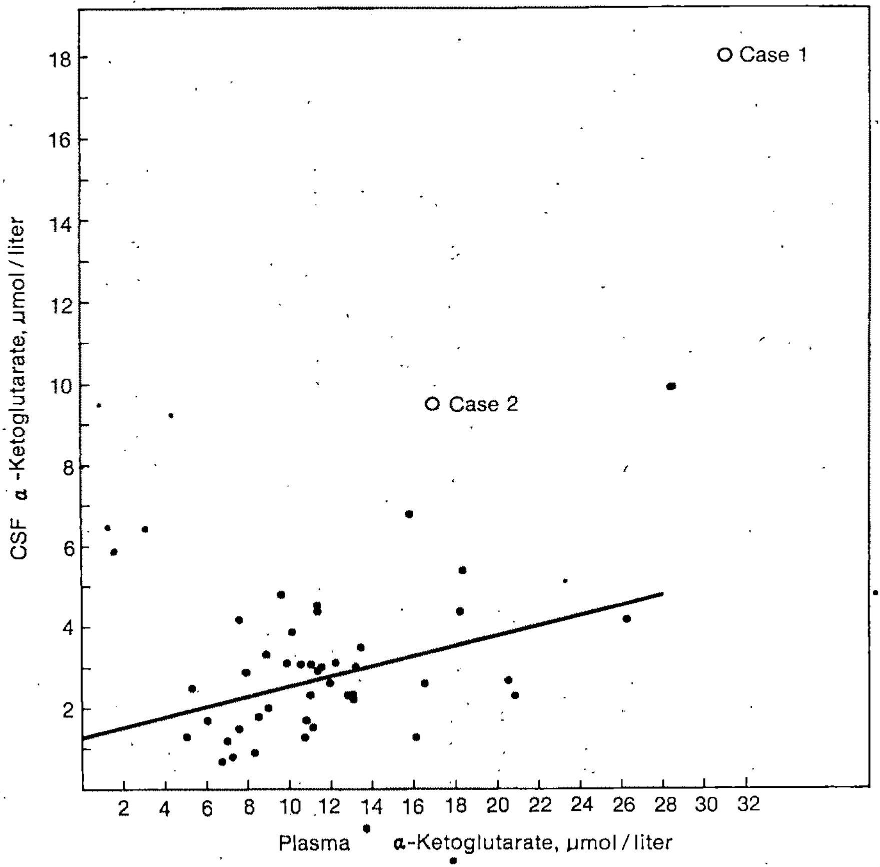


Fig 2.—Cerebrospinal fluid (CSF) pyruvate plotted vs plasma pyruvate for 43 patients including patients 1 and 2. Regression analysis gave the following: pyruvate$_{CSF}$ = 0.623 pyruvate$_{plasma}$ + 39.1; $r = 0.781$, $P < .001$. Neither case 1 or case 2 was an outlier, $P > .05$.

Fig 3.—Cerebrospinal fluid (CSF) α-ketoglutarate plotted vs plasma α-ketoglutarate for 41 patients. Regression analysis gave the following: α-ketoglutarate$_{CSF}$ = 0.125 α-ketoglutarate$_{plasma}$ + 1.31; $r = 0.422$; $P < .01$. Cases 1 and 2 were outliers at $P < .001$.



Thiamine diphosphate was measured fluorometrically.[9]

RESULTS

The value for pyruvate concentration in CSF of 119 "normal" children (Table) is very close to that reported by Svenningsen and Siesjo[10] in the CSF of 24 normal infants 3 hours to 25 days old. Levels of α-ketoglutarate were one-fiftieth as high as pyruvate.

The mean CSF pyruvate value in children with epilepsy differed from that of normal children and those with febrile seizures, but the ranges for the three groups overlapped extensively. The lower CSF α-ketoglutarate value in the nonfebrile seizure group appears to be a reflection of the older age range (Table, Fig 1).

We have also examined the CSF of 24 adults, aged 24 to 81 years, with a clinical diagnosis of possible herniated disk (Table). Both pyruvate and α-ketoglutarate values differ from these reported by Haerer[11] in the CSF of 15 normal volunteers, aged 20 to 30 years. Since the keto acids in that study were measured enzymatically in a spectrophotometer, perhaps no comparison should be made; in view of the very low values of α-ketoglutarate in spinal fluid, the increased sensitivity of the fluorometric measurement allows considerably more accuracy. Since the level of α-ketoglutarate in adult spinal fluid was significantly lower than that in children, CSF α-ketoglutarate levels were plotted as a function of age (Fig 1). In the pediatric age group, the data show a significant downward trend with age. The explanation for this age-dependent difference in CSF α-ketoglutarate is not known. A similar examination of CSF pyruvate values showed no significant trend with age in the pediatric group. Nevertheless, CSF pyruvate levels were significantly, but only slightly, lower in the two older population groups (epilepsy and herniated disk) compared with the normal children and children with febrile seizures.

To our knowledge, correlative studies of the values of the two keto acids in blood and CSF of children have not previously been reported. To determine any relationship, 42 unselected consecutive samples of blood and CSF from children with a variety of nonneurologic disorders were analyzed. In 36 of these cases, clinical diagnoses were similar to those described in normal children; four cases of febrile and two of nonfebrile seizures without apparent neurologic disease were also included. In addition, blood and CSF from a child with a progressive neurologic disease were also examined.

Values for CSF pyruvate and α-ketoglutarate in the 42 children without neurologic disease were 128 ± 7μmol/liter (range, 49μmol to 231μmol/liter) and 2.76 ± 0.21μmol/liter (range, 0.7μmol to 9.5μmol/liter), respectively; values were not significantly different from those shown in the Table. Respective levels of the two ketoacids in plasma were 146 ± 8μmol/liter (range, 54μmol to 244μmol/liter) and 11.8 ± 0.7μmol/liter (range, 5.0μmol to 26.2μmol/liter). In all 42 patients, CSF and plasma pyruvate levels were nearly equal over a fivefold range of concentration (Fig 2). Even the values in the child with proved Wernicke encephalopathy, patient 1, fell very close to the line. Nevertheless, the pyruvate values in this child were well beyond the range of normal (Table).

The CSF α-ketoglutarate levels were also proportional to plasma α-ketoglutarate concentration (Fig 3). α-Ketoglutarate levels in plasma declined with age in a pattern comparable to that in CSF (Fig 4). In contrast to the pyruvate data, the CSF α-ketoglutarate value in patient 1 deviated substantially from the regression line ($P < .001$); a similar discrepancy was seen in one of the 42 samples from children without neurologic disease, patient 2. Brief clinical reports of these two cases follow.

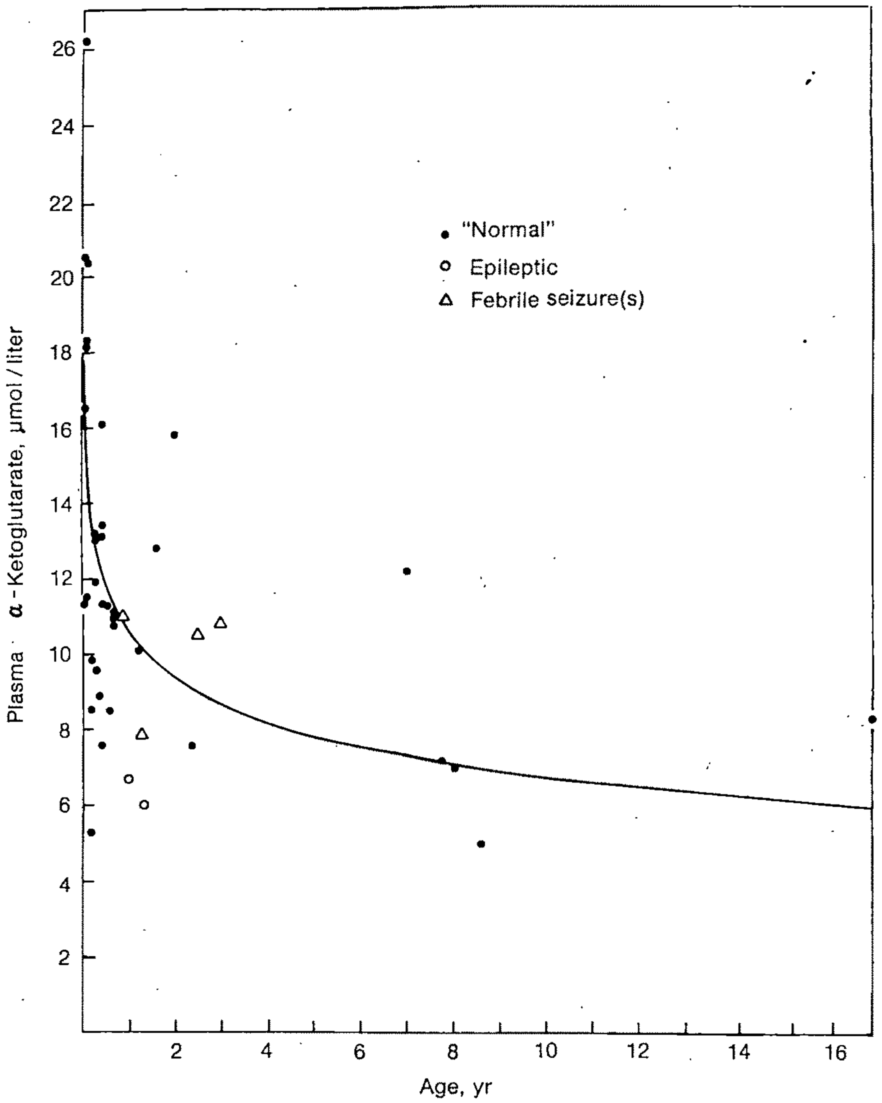


Fig 4.—Plasma α-ketoglutarate plotted vs age for 41 patients. Regression analysis of α-ketoglutarate levels vs log age gave the following: α-ketoglutarate$_{\text{plasma}}$ = −3.64 log age (in years) + 10.4; $r = 0.640$; $P < .001$.

REPORT OF CASES

CASE 1.—An 8-month-old male infant (Fig 2 and 3) with a long history of allergy was hospitalized because of vomiting, weakness, lethargy, and weight loss of 5 kg in the previous three weeks. Physical examination showed an extremely ill infant with Cheyne-Stokes respirations, pallor, edema, and hepatomegaly. There were intermittent rhythmic movements of the head, eyes, and extremities. Arterial Po$_2$ was 86 mm Hg; Pco$_2$, 20 mm Hg; and pH 7.55. The hemoglobin level was 8.7 gm/100 ml; total protein level, 6.58 gm/100 ml; and albumin content, 1.34 gm/100 ml. The CSF had no blood cells, and glucose and protein concentrations were normal.

When neurologic signs and vomiting persisted, the diagnosis of Leigh subacute necrotizing encephalomyelopathy was considered. Examination of the urine failed to show an inhibitor to thiamine diphosphate; adenosine triphosphate-phosphoryl transferase.[2-12] Because of the severe dietary restrictions for allergy and the pernicious vomiting, the possibility of Wernicke encephalopathy was investigated. Pyruvate concentration in CSF, 287μmol/liter, was more than two times the normal value, and α-ketoglutarate level, 18.0μmol/liter, was five or six times the normal value (Table, Fig 1). In plasma, pyruvate concentration was 387μmol/liter and α-ketoglutarate was 31.0μmol/liter. Thiamine diphosphate levels in red blood cells (RBCs) were not measurable (less than 25 nmol/liter) compared to 179 ± 23 nmol/liter in four controls. In CSF, thiamine diphosphate level was 2.1 nmol/liter; in the four controls, it was 9.8 ± 0.9 nmol/liter. Signs of CNS involvement improved within hours after the use of parenteral therapy with thiamine. Ten days after vitamin therapy, pyruvate and α-ketoglutarate levels in CSF and plasma and thiamine diphosphate levels in RBCs and CSF were normal.

In a 2-month-old infant with suspect Leigh disease and a positive urine test for phosphoryl-transferase inhibition,[2-12] levels of pyruvate and α-ketoglutarate in CSF did not differ from normal controls (Table). Blood was not examined in this patient.

CASE 2.—A 4-month-old infant (Fig 2 and 3) was admitted to the hospital because of cough, fever, and rapid breathing for 24 hours. Temperature was 40 C; pulse, 192 beats per minute; and respirations, 100/

min. There were intercostal and substernal retractions, and breath sounds were decreased over the right lung posteriorly. Arterial blood Po_2 was 70 mm Hg; Pco_2, 24 mm Hg; and pH 7.47. Urine pH was 7.0. Chest x-ray film showed focal infiltrates in the right lower lobe. Pyruvate concentration was 163μmol/liter in plasma and 210μmol/liter in CSF. Plasma α-ketoglutarate was also within the normal range (17μmol/liter), but the CSF α-ketoglutarate level, 9.49μmol/liter, was elevated (Table) and deviated above the regression line (Fig 3, $P < .001$). One month after discharge, repeat blood gas analysis, plasma α-ketoglutarate, and pyruvate values were normal.

In four normal adult volunteers, plasma pyruvate concentration was 78 ± 6μmol/liter and α-ketoglutarate was 5.53 ± 0.31μmol/liter. (Lumbar puncture was not performed.)

COMMENT

Levels of pyruvate and α-ketoglutarate in body fluids are easily measurable using standard fluorometric techniques. In the evaluation of progressive neurologic disease, lumbar puncture is routine; therefore, no extra risk is entailed in obtaining CSF. Furthermore, blood is usually drawn concomitantly with lumbar puncture (to compare plasma and CSF glucose levels) so that a correlation of pyruvate and α-ketoglutarate levels in the two fluids is feasible. Such data will define the relative merits of metabolite assay in the two fluids in thiamine deficiency and other metabolic or neurologic diseases. It may be that, with further experience, differences between the levels of these keto acids in blood and CSF will be useful in diagnosing a variety of metabolic diseases. For example, measurements of pyruvate and α-ketoglutarate levels in plasma and CSF should be useful in differentiating between Wernicke encephalopathy and Leigh subacute necrotizing encephalomyelopathy.[12-15] These measurements might be useful in assessing the neurologic syndromes associated with specific hereditary enzyme defects of pyruvate carboxylation or decarboxylation.[2-7] In enzymatic deficiencies of pyruvate carboxylase or decarboxylase, pyruvate levels alone would not be discriminatory. However, with reduced levels of pyruvate decarboxylase, but not in pyruvate carboxylase deficiency, levels of α-ketoglutarate and other substrates below the metabolic block would be expected to be reduced.

It is well known that hypocapnia and alkalosis are associated with elevations of pyruvate and lactate levels in blood.[16-21] Levels of α-ketoglutarate in blood during hyperventilation have not previously been investigated in human beings. However, experimental evidence suggests that they might also be affected: both pyruvate and α-ketoglutarate levels increased significantly in the brains of rats hyperventilated to reduce arterial CO_2 tensions and increase plasma pH.[22] This possibility was considered as an explanation for the elevated CSF α-ketoglutarate level in the child with hypocapnia associated with hyperventilation and pneumonia (patient 2). However, the relatively low level of plasma pyruvate did not support this explanation. Since episodic hyperventilation is a common accompaniment of clinical central nervous system disease, these findings suggest caution in relating abnormal levels of these metabolites (pyruvate, lactate, α-ketoglutarate) primarily or exclusively to hereditary enzymic defects and inhibitions or to acquired vitamin deficiency. Nor can it be said to what degree hypocapnia and respiratory alkalosis may have contributed to the elevated plasma and CSF pyruvate and α-ketoglutarate levels in the child with proved Wernicke encephalopathy. Nevertheless, the methods of measurement of pyruvate and α-ketoglutarate presented here are simple, rapid, and reproducible. Coupled with appropriate measurements of arterial Po_2, Pco_2, lactate, and blood and urine pH, and the above considerations, they are proposed as useful screening tests in evaluating infants and children with progressive neurologic disease of unknown cause.

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Barbara Hixon, Division of Biostatistics, Washington University School of Medicine, assisted with the statistical interpretation of the data, Sandy Simmons performed some of the metabolite assays, and Jonathan H. Pincus, MD, performed the urinalysis in case 1.

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Hypersomnia With Periodic Apneas in Acquired Micrognathia

A Bird-like Face Syndrome

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• We describe a syndrome characterized by acquired micrognathia, hypersomnia, and periodic apneas during sleep. Six patients affected with the syndrome underwent nocturnal and diurnal polygraphic recordings that demonstrated that during sleep there is an uninterrupted succession of apneas, primarily the obstructive type, analogous to those observed in Pickwickian syndrome. Simultaneous recording of pulmonary and systemic arterial pressure during sleep and repeated blood gas analyses have shown that as soon as the apneas appear there is a decisive increase in pulmonary and systemic pressure and serious alveolar hypoventilation. The hemodynamic and ventilatory changes are even more intense during rapid eye movement sleep. Tracheostomy, performed on five of our patients, is the only treatment producing complete clinical remission of the syndrome.

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Acquired micrognathia is a consequence of osteomyelitis or fractures of the mandibular condyles occurring in early childhood. The mandibular underdevelopment gives the patient a bird-like face, while the concomitant ankylosis of the temperomandibular joints, which restricts mouth opening, may cause serious difficulties in food intake.

A rare complication of acquired micrognathia is the appearance of a clinical picture characterized by hypersomnia, periodic apneas during sleep, and alveolar hypoventilation. The first clinical description of this syndrome was reported by Valero and Alroy[1]; their patient recovered after undergoing tracheostomy with the placement of a permanent tracheal cannula. Hence these authors ascribed the pathogenesis of the syndrome to incomplete obstruction of the upper airways due to retroposition of the tongue, caused by the micrognathia.

After this first description, a few similar cases studied by polygraphic recording methods were reported.[2-4] The polygraphic findings confirmed that these patients had, in addition to marked hypersomnia, apneas of a prevalently obstructive type that appeared at dozing off and repeated uninterruptedly throughout sleep. Tracheostomy has proved to be the only treatment capable of reversing the symptoms.

This article presents the clinical and polygraphic data from six patients with hypersomnia with periodic apneas secondary to acquired micrognathia. One of these patients (No. 6) has already been described in a previous report.[4]

SUBJECTS AND METHODS

Table 1 summarizes the clinical findings. All six patients had stereotyped symptoms: micrognathia acquired during childhood

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Table 1.—Clinical and Laboratory Data on Six Patients

Patient/Age, yr/sex	Cause of Micrognathia	Age at Onset	Respiratory Disturbance During Sleep	Hypersomnia
1/50/M	Osteomyelitis	3 yr	Loud snorer from age 6 or 7; apneas during sleep from same age	Diurnal somnolence from age 8 or 9; sudden increase in somnolence from age 45
2/40/M	Osteomyelitis	6 yr	Loud snorer from age 6; intermittent snoring and restless sleep from age 24	Diurnal somnolence from age 24; rapid increase in somnolence from age 36
3/52/M	Osteomyelitis	10 mo	Loud snorer from early infancy; weight gain (10 kg); restless sleep, apneas from age 50	Diurnal somnolence from age 50
4/11/M	Osteomyelitis	6 mo	Loud snorer from age 1; apneas during sleep from age 6	Diurnal somnolence from age 9
5/52/M	Osteomyelitis	4 yr	Loud snorer from age 5; apneas during sleep from age 7 or 8	Diurnal somnolence from age 25; rapid increase in somnolence from age 48
6/65/F	Fracture of both mandibular condyles	3 yr	Loud snorer from early infancy; apneas during sleep from age 60	Diurnal somnolence from age 61; rapid increase in somnolence from age 64

*Electrocardiogram.

gave a bird-like face (Fig 1) and was accompanied by diurnal hypersomnia and recurrent apneas during sleep. Ankylosis of the temperomandibular joints was present in all the patients: the maximum mouth aperture at the level of the anterior dental arch ranged from 0.5 to 1.5 cm. In all cases, respiratory difficulty during sleep, represented by heavy snoring, had been present from the time when the micrognathia occurred; the onset of the sleep apneas followed the mandibular lesion by intervals varying from a few years to many decades.

The apneas were generally described by a spouse or a relative who slept near the patient as intermittent respiratory arrests, during which the patient appeared to be suffocating and made violent, ineffective respiratory efforts. At the end of the apnea, which was estimated to last a minute more or less, the patient snored noisily and moved about violently. Cyanosis was noted during the apneas in four patients. The patient himself could determine approximately when the apneas set in because from that moment his sleep became agitated, and he awoke frequently with the sensation of suffocating. Three patients constructed raised sides for their beds because breathing efforts were sometimes so violent that they fell out of bed.

In a few patients, the diurnal hypersomnia seemed to follow the onset of the apnea, but in others the two appeared to begin concurrently. In all patients the hypersomnia remained temporarily stationary or worsened slowly, then suddenly became more severe, simultaneously with a deterioration in nocturnal breathing. On admission to our clinic, all the patients slept almost continuously whenever left

Physical Examination	Cardiorespiratory Data	Roentgenographic Studies
Micrognathia; height, 163 cm; weight, 60 kg; anteroposterior flattening of thorax with deep transverse depression at level of insertion of diaphragm	ECG*: right atrial overload, right ventricular hypertrophy, incomplete right bundle branch block Respiratory function: normal, slight hypoventilation	Thoracic: moderate enlargement of right heart and prominence of pulmonary arch Mandible: hypoplasia of mandible and deformation of condyles, ankylosis of temperomandibular joint
Micrognathia; height, 169 cm; weight, 62 kg, transverse depression of thorax at level of insertion of diaphragm; slight pitting edema of ankles; liver palpable about two fingers below costal margin	ECG: right atrial overload, right ventricular hypertrophy Respiratory function: normal; alveolar hypoventilation	Thoracic: increase of right section of heart Mandible: marked hypoplasia of mandible with complete obliteration of joints
Micrognathia; height, 167 cm; weight, 75 kg	ECG: left ventricular hypertrophy Respiratory function: moderate restrictive syndrome; slight alveolar hypoventilation	Thoracic: thickening of right pleura; increased bronchovasal markings Mandible: hypoplasia of the mandible; especially the right half; complete absence of right condyle, which appears to be replaced by fibrous tissue
Micrognathia; height, 145 cm; weight, 48 kg; transverse depression of thorax at level of insertion of diaphragm	ECG: right atrial overload Respiratory function: normal, normal alveolar ventilation	Thoracic: normal Mandible: underdevelopment of mandible, especially right half; absence of right condyle and sclerosis of right temperomandibular joint; hypoplasia of left mandibular condyle
Micrognathia; height, 166 cm; weight, 65 kg	ECG: atrial flutter with unstable block 8/1 to 4/1 (during sleep, 10/1 to 15/1); slight left ventricular hypertrophy Respiratory function: normal; mild alveolar hypoventilation; reduction of ventilatory response to carbon dioxide	Thoracic: normal Mandible: serious mandibular underdevelopment with complete obliteration of temperomandibular joint
Micrognathia; height, 155 cm; weight, 65 kg	ECG: normal Respiratory function: normal; normal alveolar ventilation	Thoracic: normal Mandible: mandibular hypoplasia with partial ankylosis of temperomandibular joint

undisturbed. One patient had to walk to remain awake, another managed to sleep for short periods leaning against a wall, and three others fell asleep during meals.

Two patients (No. 2 and 4) had undergone plastic surgery to lengthen the mandibular branches, without appreciable results. A third patient (No. 1) was supposed to undergo the same operation, but stopped breathing and became cyanotic after receiving the preanesthetic medication. He was immediately tracheotomized and resuscitated; the tracheal stoma was closed a few hours later and the operation was not performed.

None of the patients was obese, but in one (patient 3) hypersomnia and respiratory disturbance worsened in conjunction with a weight increase of about 10 kg.

Three patients had mild alveolar hypoventilation during wakefulness; two of these showed electrocardiographic or radiological signs of right heart involvement.

Blood cell counts and hematocrit levels were normal in all subjects. In no case did respiratory function tests account for the alveolar hypoventilation. In one patient (No. 5) the ventilatory response to hypercapnia was studied by inhalation of a mixture of 5% and 7% carbon dioxide in room air, the response was markedly diminished, since ventilation increased by only 250 ml/min for every millimeter of mercury of increase in the Pa_{CO_2}.

Two patients (No. 1 and 2) underwent cineradiographic studies of the oropharyngeal region during sleep; these studies demonstrated that during apnea the oropharyngeal wall collapsed and obstructed the upper airway.

Treatment

Tracheostomy was performed in five patients and immediately relieved clinical symptoms. In all patients electrocardiographic signs of atrial and right ventricular overload and atrial flutter (patient 5) disappeared within a few days after the operation.

The tracheostomy, after postoperative periods ranging from seven months to six years, has been well tolerated by all the patients, and no complications have ensued. The tracheal stoma, kept closed during the day to permit the patients to speak normally, is opened at night to bypass the upper airway obstruction.

Polygraphic Studies

All of the patients underwent at least one polygraphic recording during spontaneous nocturnal sleep; in five cases, the recording was continued for 24 hours. The polygraphic recordings included simultaneous recording of the electroencephalogram, the horizontal electro-oculogram, the electromyogram of the mylohyoid muscle, the ECG, and the electromyogram of an intercostal muscle recorded by means of surface electrodes at the level of the right tenth intercostal space. Air flow through the upper airways was recorded by means of thermocouples placed in front of the mouth and in one nostril. Thoracic movements were recorded using an expandable tube attached to a belt around the thorax and connected to a piezoelectric transducer. Snoring was recorded by a microphone suspended over the patient's head.

Four patients underwent a subsequent nocturnal polygraphic recording during which, in addition to the previous variables, the endoesophageal pressure was recorded from a catheter equipped with a terminal ballon placed in the lower third of the esophagus.[5]

Two patients underwent an additional nocturnal polygraphic recording that included the pulmonary and the systemic arterial pressures; in three patients only the systemic arterial pressure was recorded, and in one, only the pulmonary

Table 2.—Relative Percentage and Duration of Different Types of Apneas and Percentage of Time Spent in Apnea in Sleep Stages*

Sleep Stage	Time Spent in Apnea, %†	Frequency of Apnea %†			Length of Apnea, sec†		
		Central	Mixed	Obstructive	Central	Mixed	Obstructive
1	39(24-60)	10.6(0-20)	24.8(9-55)	64.6(24-91)	11(6-20)	30(8-60)	22(6-40)
2	52(39-74)	1(0-3)	8.4(3-13)	90.6(84-96)	10(6-15)	27(10-60)	28(8-72)
3-4	51(44-79)	0	0	100	...	...	25(12-50)
REM‡	58(39-77)	4.5(0-9)	12.4(5-27)	83.1(63-95)	12(6-20)	40(20-110)	37(8-76)
Total sleep	51(39-73)	3(0-5)	11(3-17)	86(77-96)	11(6-20)	29(8-110)	28(6-76)

*Average values of six patients.
†Numbers in parentheses indicate extreme values.
‡Rapid eye movement.

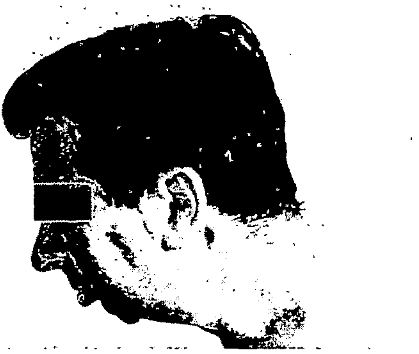
Fig 1.—Patient 1. Micrognathia gives bird-like profile.

pressure. The systemic arterial pressure was recorded by percutaneous cannulation of a radial artery with Teflon tubing connected to a pressure transducer; a stopcock permitted intermittent irrigation and blood sampling. Blood samples were taken many times in the course of the night in different sleep stages; each sample was drawn slowly during the course of an apnea and during the subsequent resumption of ventilation. The samples were analysed immediately by a gas analyser.

The pulmonary artery pressure was recorded by means of a floating microcatheter introduced through an antecubital vein into the pulmonary artery and connected to a pressure transducer. A three-way stopcock permitted periodic irrigation of the catheter.

The nocturnal recordings were carried out with the patient in a comfortable bed in an air-conditioned, quiet room. The recording apparatus was in an adjoining room. During the day, the patient sat in a comfortable armchair in the same room used for the nocturnal recordings. If the patient desired, the recording was interrupted periodically to allow short walks.

The sleep stages were classified according to the criteria suggested by Rechtschaffen and Kales,[6] except that stages 3 and 4 of deep slow sleep were lumped together.

Using the same polygraphic recording methods, we also studied, in a few normal individuals, the physiological variables studied in patients during sleep. Nocturnal sleep was studied in eight men between the ages of 25 and 45, for a total of 21 recordings. The systemic arterial pressure and arterial blood gas analysis values were determined in eight men from 28 to 68 years old, while the pulmonary artery pressure was recorded in four men and one woman from our laboratory staff, aged 30 to 50 years. The values of the normal subjects are reported in the Tables as controls and the extreme values are given in parentheses.

RESULTS

The results of these polygraphic investigations are synthesized in Tables 2 and 3.

Sleep Disturbance

The presence of a marked diurnal hypersomnia was demonstrated in all of the patients who underwent a 24-hour recording; they slept an average of 16 out of 24 hours. During the day, the sleep episodes lasted from a few minutes to several hours. The deep slow sleep stages (stages 3 and 4), which are quite scarce at night (average, 8%; control group, 29%), were more abundant during daytime sleep when the patient slept in an armchair and his breathing improved (average, 17%); the rapid eye movement (REM) stage occurred in almost normal percentages during both nocturnal (average, 22%; control group, 23%) and diurnal (18%) sleep. In all patients the EEG tracing in wakefulness or in sleep was normal.

Respiratory Disturbance

Apnea appeared in all patients as soon as they fell asleep and recurred uninterruptedly throughout sleep (Table 2). The apneas were separated by a few extremely noisy respiratory movements. When breathing resumed, sleep lightened and a short arousal was observed. Three types of apnea were observed:

1. Central, a complete respiratory arrest; during such apnea thoracic movements and oscillations of the endoesophageal pressure are absent. This was the least frequent (about 3%) and least prolonged (average duration, 11 seconds) type; central apneas occurred almost exclusively during light sleep (stages 1 and 2) and REM sleep.
2. Obstructive, in which the flow of air through the upper airways ceases, while the thoracic movements persist and intensified progressively until the end of the apnea; the ineffective inspiratory efforts were recorded by the accentuation of the intercostal muscle activity and by the progressive increase in the negative endoesophageal pressure, which, at the end of the apnea, could reach 70 to 80 cm of water pressure (Fig 2); these apneas were the most numerous (average, 86%) and prolonged (average, 28 seconds).
3. Mixed, or central apnea followed by obstructive apnea (Fig 2). These apneas constituted about 11% of the total, and had an average duration of 29 seconds. The longest apneas were consistently observed during REM sleep, where they could last as long as 90 to 110 seconds.

One patient (No. 3) experienced incomplete nocturnal obstructive apneas; the thermocouples indicated that some air always flowed through the mouth or nostrils. The upper airway obstruction was also incomplete in the other patients during the daytime recordings when they were

Table 3.—Pulmonary and Systemic Arterial Pressure and Blood Gas Analysis Values During Wakefulness and Sleep Before Tracheostomy

		Sleep Stage			
Patient	Waking	1	2	3-4	REM*
1 Systemic arterial pressure, mm Hg	156/90	171/103	193/112	203/111	205/113
Pulmonary artery pressure, mm Hg	45/23	56/33	68/43	88/57	100/64
Mean	32	36	54	63	70
PaCO$_2$, mm Hg	52	. . .	58.5	65.6	66.6
PaO$_2$, mm Hg	74.6	. . .	60	58.6	53
pH	7.36	. . .	7.34	7.30	7.30
SaO$_2$, %	94.2	. . .	89	86.5	81
2 Systemic arterial pressure, mm Hg	125/94	136/99	133/98	133/99	144/102
Pulmonary artery pressure, mm Hg	46/22	63/30	79/39	84/44	98/58
Mean	29	. . .	. . .	58	70
PaCO$_2$, mm Hg	59	. . .	65	68	70.7
PaO$_2$, mm Hg	71	. . .	58	56	45
pH	7.33	. . .	7.30	7.30	7.27
SaO$_2$, %	92.7	. . .	85.8	84	72
3 Systemic arterial pressure, mm Hg	226/114	232/118	248/130	258/137	235/127
PaCO$_2$, mm Hg	40.5	44	44.2	41.6	. . .
PaO$_2$, mm Hg	69.5	58	57	58	. . .
pH	7.37	7.33	7.32	7.34	. . .
SaO$_2$, %	93.2	89	86.3	87.5	. . .
4 Systemic arterial pressure, mm Hg	118/85	134/97	138/101	131/96	154/112
PaCO$_2$, mm Hg	36.5	. . .	40	47.4	50.5
pH	7.38	. . .	7.33	7.30	7.27
5 Systemic arterial pressure, mm Hg	167/95	193/107	197/108	192/103	201/109
PaCO$_2$, mm Hg	51	53	57.5	63	61.3
PaO$_2$, mm Hg	73	70.5	61.2	60	48.6
pH	7.33	7.32	7.30	7.27	7.28
SaO$_2$, %	93.5	92.2	86.7	86	77.6
6 Pulmonary arterial pressure, mm Hg	33/17	41/22	54/31	57/33	73/40
PaCO$_2$, mm Hg	38	. . .	49	. . .	. . .
PaO$_2$, mm Hg	90	. . .	56	. . .	. . .
pH	7.39	. . .	7.32	. . .	. . .
SaO$_2$, %	97	. . .	86	. . .	. . .
Normal subjects† Systemic arterial pressure, mm Hg	129,14/60.28	125.15/57.28	118.86/54.85	112/52.14	120.8/58.8
Pulmonary artery pressure, mm Hg	18/8.5(27/10-13/5)	19.5/9(28/13-13/4)	23/11(28/14-19/5)	23.5/12(31/14-21/6)	23/11(31/14-20/6)
PaCO$_2$, mm Hg	36.3(33-39.5)	38(35-40)	39.5(36-42)	39.4(36-42.3)	39.3(35.5-42)
PaO$_2$, mm Hg	81.3(70-93.2)	74(65-84)	77(70-85)	77.8(65.5-83)	78.7(64-88)
pH	7.36(7.34-7.39)	7.35(7.34-7.38)	7.33(7.28-7.37)	7.33(7.28-7.35)	7.33(7.29-7.36)
SaO$_2$, %	95(92-97)	94(92-96)	94.4(93-96)	94.4(91-96)	94.2(91-96)

* Rapid eye movement.
† Numbers in parentheses indicate extreme values.

sleeping sitting in an armchair with the head bent forward.

Alveolar Ventilation

Respiratory function tests in all patients showed no abnormalities in pulmonary volumes or respiratory mechanics. Table 3 gives arterial blood gas values during wakefulness and sleep. During wakefulness blood gas values were normal in three patients; the other three had hypercapnic acidosis.

During sleep, alveolar hypoventilation that increased progressively through the successive stages of slow sleep (from stage 2 through stage 4) and underwent a further increase in REM sleep developed in five patients. In the patient (No. 3) with incomplete obstruction of the airways, the alveo-

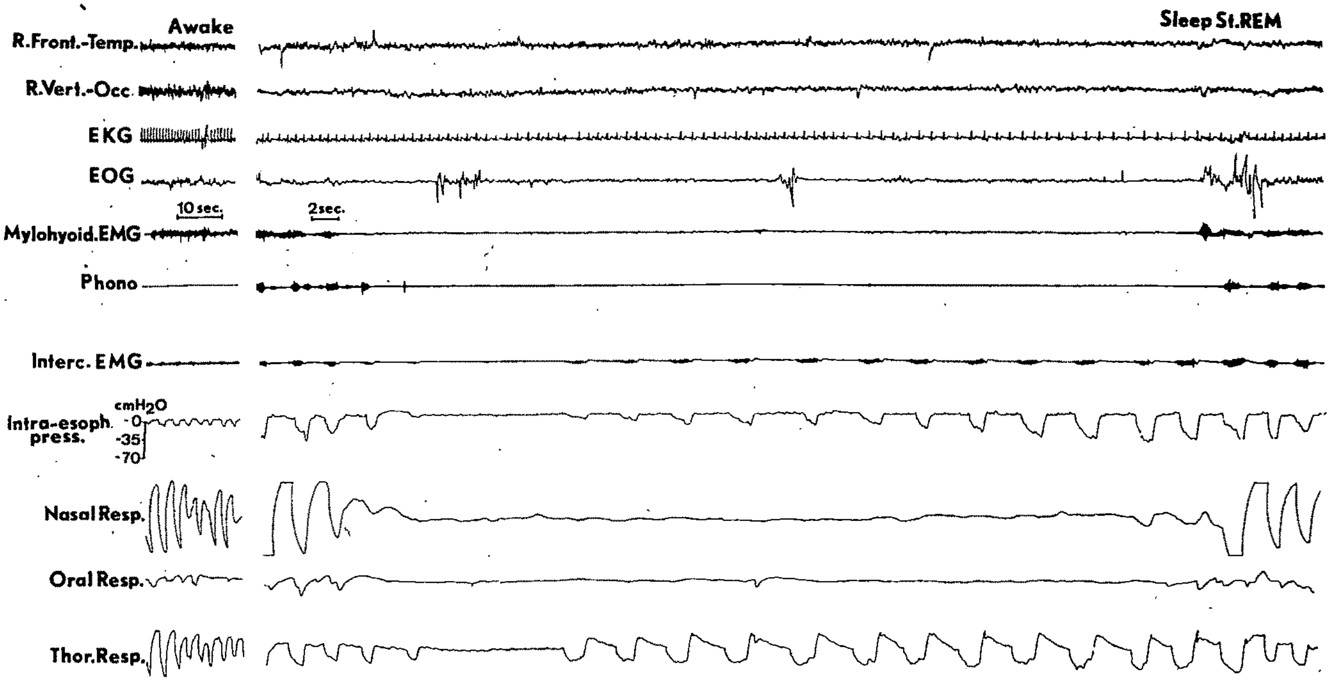

Fig 2.—Patient 1. Left, Regular breathing during wakefulness. Right, Mixed apnea during rapid eye movement sleep. On resuming ventilation, patient snores loudly because incomplete obstruction of upper airways persists. Heart rate slows during apnea; when ventilation resumes, tachycardia occurs.

lar hypoventilation during sleep was mild or absent.

Systemic and Pulmonary Arterial Pressure

In all subjects, the systemic arterial pressure rose progressively from stage 1 through stage 4 and, in four patients, underwent a further increase in stage REM (Fig 3, Table 3). In the three patients in which it was measured, the pulmonary artery pressure increased in all the sleep stages and reached its highest values during REM sleep. During obstructive apnea, pulmonary artery pressure underwent wide oscillations synchronous with the ineffective respiratory movements. During nocturnal arousals and at awakening in the morning, pressure values returned to usual waking values within one or two minutes.

Polygraphic Recordings After Tracheostomy

Polygraphic recordings carried out in four of the five patients at various intervals after tracheostomy demonstrated in all that, after only a few days, nocturnal sleep returned to a normal pattern and diurnal sleep disappeared. In two cases, sporadic central apneas lasting five to ten seconds during light sleep (stages 1 and 2) lasted for several months postoperatively.

At intervals from 5 to 15 days after the operation, four patients underwent a polygraphic recording with recording of systemic arterial pressure and, in three cases, with pulmonary artery pressure. In all instances systemic arterial pressures during sleep remained at or below waking levels.

During wakefulness, the pulmonary artery pressure returned to normal or near normal values in all the patients, but during sleep a slight degree of hypertension was still present. Blood gas values remained normal in all patients during sleep.

Three years after tracheostomy, the tracheal stoma was kept totally closed for ten days (and nights) in one patient (No. 6), during which time three polygraphic recordings were carried out during nocturnal sleep. The obstructive apneas reappeared during stages 1 and 2 and REM sleep the very first night that the tracheal stoma was kept closed; in the final recording on the tenth night, the apneas had become almost continual throughout the sleep period.

COMMENT

All these patients had obstructive or mixed apnea that appeared with dozing off and recurred uninterruptedly throughout the sleep period. These apneas were different from those observed in normal individuals on falling asleep.[7] Physiological apneas are, in fact, sporadic, or occur in series lasting only a few minutes, and generally arise during light sleep (stages 1 and 2), rarely during REM sleep. They are of short duration (10 to 20 seconds) and are exclusively central; more often it is a question of hypopnea (wavelike breathing).

In five patients, alveolar hypoventilation appeared during sleep, or worsened if it was already present during wakefulness. Hypoventilation during sleep in normal subjects has been observed by some authors,[8,9] but this finding has not been confirmed by others.[10,11] In our control group (Table 3) we did encounter a significant rise in the Paco_2 values during sleep as compared to wakefulness, but in no case did the Paco_2 values rise beyond physiological levels, Bulow[7] made analogous findings. Hence, the alveolar hypoventilation of our patients resulted from the apneas and not from sleep. This inference is confirmed by the fact that, after tracheostomy and the disappearance of apnea, the $Paco_2$ value did not rise above physiological levels during sleep.

In the normal subjects the pulmonary artery pressure increased during sleep, but did not rise above physiological values (Table 3). In contrast, the pressure values of the patients reached pathological levels. The pulmonary artery pressure increase can be attributed partly to the blood gas changes, but may also be partly due to hemodynamic changes caused by endothoracic pressure variations during ineffectual inspiratory efforts during obstruction. The persistence of pulmonary hypertension after tracheostomy could reflect anatomical modifications of the pulmonary vessels secondary to the chronic hypertension.

The systemic arterial pressure rose in all of the patients during sleep, contrary to the normal pattern.[12] The increase probably is due to abnormal intrathoracic hemodynamic conditions resulting from obstruction, rather than being caused by hypoxia or hypercapnia. A similar systemic arterial pressure rise occurred in patient 3, who had no alveolar hypoventilation during sleep.

After tracheostomy the base pressure values diminished, and during sleep they showed the same pattern of behavior as those of normal subjects.

The polygraphic study of our patients, like the studies of those of Hishikawa et al[2] and Tammeling et al,[3] has demonstrated that the sleep and respiratory disturbances that can appear in acquired micrognathia are identical to those that are found in the so-called cardiorespiratory syndrome of obesity,[13,14] in primary alveolar hypoventilation,[14] and in patients with an anatomical obstruction of the upper airways due to laryngeal stenosis.[15] The clinical descriptions of some patients described in the literature lead us to believe that the hypnorespiratory disturbances encountered in some children with tonsillar and adenoidal hypertrophy are analogous

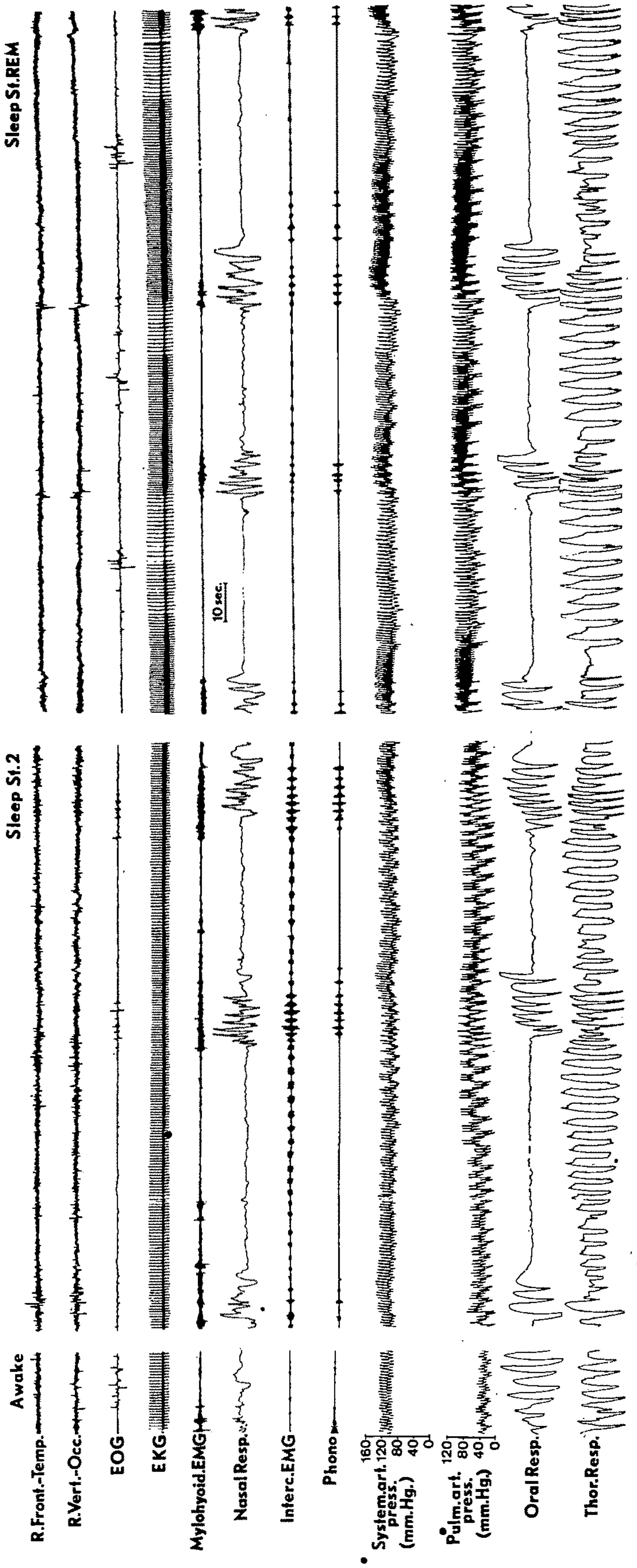

Fig 3.—Patient 2. Pulmonary and systemic arterial pressure during wakefulness and sleep. During sleep, when uninterrupted series of obstructive apneas occur, arterial pressure, especially of pulmonary artery, increases considerably. Highest pressure values are reached during rapid eye movement sleep at end of each apnea.

to those observed in our patients.[16-18] Consequently, we have proposed to group all these conditions under the syndrome "hypersomnia with periodic apneas."

Eliminating the obstruction of the upper airways, whether by weight loss (as in Pickwickian syndrome), by surgical removal of the anatomical obstacle to respiration, or by tracheostomy, leads to remission of the syndrome, establishing that the obstructive apneas during sleep are the principal cause.

Prior to presenting a fully developed form of the syndrome, all of our patients had been heavy snorers for years. In a recent article[19] we demonstrated that heavy snoring is accompanied by an incomplete obstruction of the upper airways, the presence of numerous obstructive apneas during sleep, and, often, mild alveolar hypoventilation. Very probably, the increased energy cost of breathing required to overcome the resistance created by the upper airway obstruction induces the organism to adapt to a certain degree of hypoventilation.

The hypercapnia thus produced could cause a diminution (or further diminution) of the respiratory center sensitivity to carbon dioxide, with progressive accentuation of the apnea and alveolar hypoventilation. Indeed, it has been noted that not only chronic hypercapnia,[20] but also the intermittent hypercapnia of underwater swimmers[21] diminishes the ventilatory response to carbon dioxide. The progressive reduction in the excitability of the respiratory center then leads to a state of alveolar hypoventilation during wakefulness.

It remains to be explained why this type of self-aggravating respiratory disturbance does not arise in all cases where marked obstruction of the upper airways is present during sleep. Perhaps, in subjects in whom severe hypnorespiratory disturbances develop, a primary hypoexcitability of the respiratory center exaggerates the normal tendency to breathe periodically during sleep and creates a marked hypnogenic hypotonia of the oropharyngeal musculature. The excitability of the respiratory center varies greatly in normal subjects, but in the patient we tested the ventilatory response to carbon dioxide was clearly below the physiological range.

The hypoexcitability of the respiratory center, whether primary or secondary to the chronic hypercapnia, explains why these patients are susceptible to respiratory arrest when small doses of sedative drugs are administered, as, for example, preoperative medication (patient 1).[2]

The hypnogenic hypotonia of the oropharyngeal muscles and their valve mechanism contributes to a collapse of the oropharyngeal walls; this has been demonstrated cineradiographically in two of our patients and in some patients with Pickwickian syndrome.[22,23] Diurnal hypersomnia in these patients can be considered a consequence of poor nocturnal rest resulting from the repeated arousals occurring at the end of each apnea.[13] However, it is possible that, like the hypoventilation, the hypersomnia is linked to a primary or acquired hypoexcitability of the reticular activating system. Indeed, the chronic hypercapnia could progressively depress not only the respiratory center but also the reticular activating substance, which is also sensitive to carbon dioxide.[24]

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Cerebral Ischemic Events Associated With Prolapsing Mitral Valve

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• Twelve patients who had no evidence of arteriosclerotic cerebral vascular disease, lacked hypertension or coagulation defect, and had not been receiving contraceptive therapy had recurrent transient cerebral ischemic attacks (TIAs) and partial nonprogressive strokes. All had prolapsing mitral valve proved by angiocardiography. The average age was 38 years, compared with 62 years in a larger series of patients with TIA associated with arteriosclerosis. We propose that the ischemic events are related to emboli emanating from the abnormal mitral valve with or without an associated paroxysmal cardiac arrhythmia.

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The recognition and cardiovascular expression of prolapsing mitral valve (PMV) have received increasing attention since the first descriptions by Fernex and Fernex in 1958,[1] by Reid in 1961,[2] and elaboration by Barlow et al in 1963.[3] Although initially described as benign, more recent reports[4-12] demonstrate arrhythmias and postexercise arrhythmias, significant mitral regurgitation, bacterial endocarditis, and a propensity to sudden death. The incidence of the condition and factors that distinguish a benign from a serious lesion are unsettled. Two recent echocardiographic studies in "normal" young adults give an incidence in men of 0.5% and in women of 6%.[13,14] Neurological disturbances occurring in patients with this disorder have been noted in passing,[15,16] but never, to our knowledge, described previously in detail. This report concerns transient and persistent cerebral ischemic events in 12 patients with PMV.

SUBJECTS AND METHODS

The subjects were found during a prospective treatment trial with platelet-inhibiting drugs in patients with transient ischemic attacks (TIAs) and partial nonprogressing strokes. All patients with these events and with normal angiograms or with an abnormality on the angiogram that would not explain the cerebral or retinal symptoms were subjected to carefu cardiac scrutiny. Detailed history with respect to chest pain, palpitations, and awareness of irregular heart action was sought. Careful auscultation for systolic clicks and murmurs was coupled with phonocardiography. All patients were submitted to routine ECGs supplemented by 24 to 72 hours of cardiac monitoring. Echocardiography was done routinely, and when it or the other findings suggested PMV angiocardiography was carried out.

Patients were eliminated from consideration for this report if cerebral angiography showed significant extracranial or intracranial atherosclerotic arterial disease. All patients were studied for abnormalities of platelets and coagulation mechanisms, and none were found with this association. Patients with coronary artery disease as judged by history, ECG, and, in most instances, from studies by coronary angiography were excluded.

REPORT OF CASES

Case 1.—A girl, aged 10 years, in 1966 suffered an acute left hemiplegia, with complete recovery. Cerebral angiography demonstrated an occluded right middle cerebral artery, proximally. In 1968, a similar attack occurred. In 1975, when the patient was 18 years old, left-sided numb-

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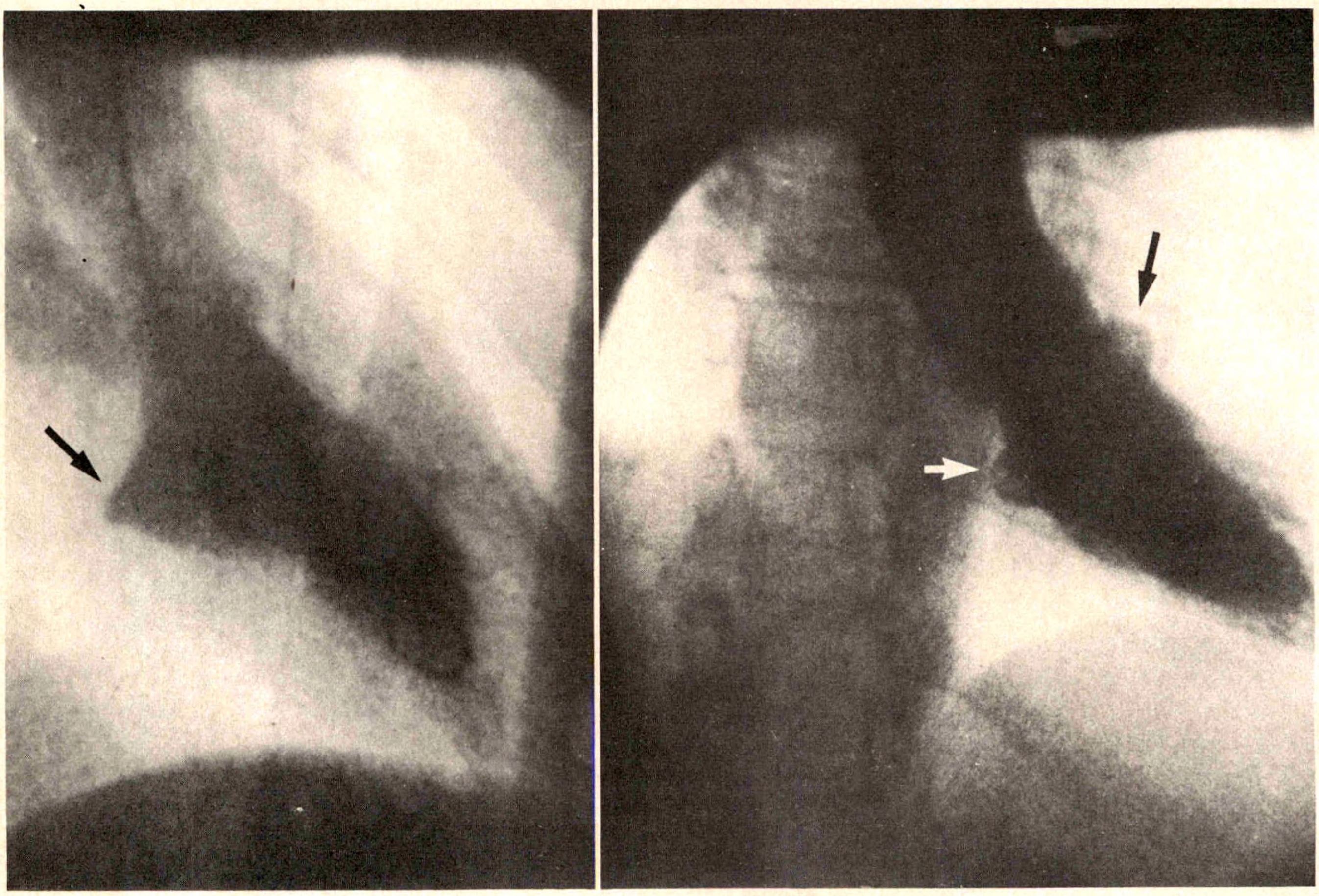

Fig 1.—Left ventricular angiograms, right anterior oblique projections. Left, Normal flat systolic closure line (arrow) at right angle to inferior ventricular wall. Right, Mitral valve prolapse with systolic bulging of closure line, in this example (case 2), posteromedial and anterolateral commissural scallop prolapse (arrows).

ness, blurred vision, and leg awkwardness developed over several hours. Examination showed a right homonymous hemianopsia and a mild left-sided spastic weakness, with slight reduction in left-sided cortical sensory modalities. Bilateral carotid arteriograms and vertebral angiogram were normal, and the previously occluded artery was patent. She had no cardiac symptoms, but had a midsystolic click and a midsystolic ejection murmur. The resting ECG was normal, but 24-hour monitoring showed periodic attacks of sinus tachycardia up to 140/min. Echocardiogram was in keeping with a PMV, and this was confirmed by cardiac catheterization. At the time of discharge, the hemianopsia persisted.

Case 2.—In August 1975, a 19-year-old man was afflicted with the abrupt onset of paralysis of the left arm, followed within an hour by a transient weakness of the leg. Physical examination indicated minimal left facial droop and left flaccid arm weakness. An EEG delta-wave focal abnormality was present in the right central parietal area. There was an early systolic murmur at the apex. Electrocardiographic monitoring and echocardiography were normal. Angiocardiography determined a prolapse of both the posteromedial and the anterolateral commissural scallops of the posterior leaflets of the mitral valve (Fig 1). Right vertebral and bilateral carotid angiograms were free of arteriosclerotic changes, but there was terminal occlusion of the temporal branch of the left middle cerebral artery. After three months, recovery was good, except for minimal arm spasticity and impaired fine finger movement.

Case 3.—A 20-year-old man developed an awareness of very irregular heart action in May 1974. Within an hour, he developed severe vertigo, lost the hearing in his left ear, and was unable to walk because of dizziness and ataxia. Atrial fibrillation was detected, which reverted spontaneously to normal sinus rhythm in ten hours. Within three days, his vertigo and gait disturbance disappeared, but hearing loss persisted. During the next year, he had three 5- to 10-minute bouts of atrial fibrillation.

In July 1975, echocardiography indicated a PMV, with ventricular angiography demonstrating moderate prolapse of the posteromedial commissural scallop of the posterior leaflet. The coronary and cerebral arteries were not examined. He was given propranolol hydrochloride, and for nine months he has been free of atrial fibrillation.

He continues to exhibit loss of left auditory function and only a minimal left vestibular response to a strong stimulus; these findings are compatible with left internal auditory artery ischemia.

Case 4.—A woman, aged 34 years, after taking an oral contraceptive for six years, awoke in July 1973 with right hemiplegia and aphasia. Forty-eight hours later, angiography indicated an occlusion of a Sylvian branch of the left middle cerebral artery, with early filling of the veins in the area of speech and motor function. She made substantial recovery within one week and discontinued contraceptive therapy.

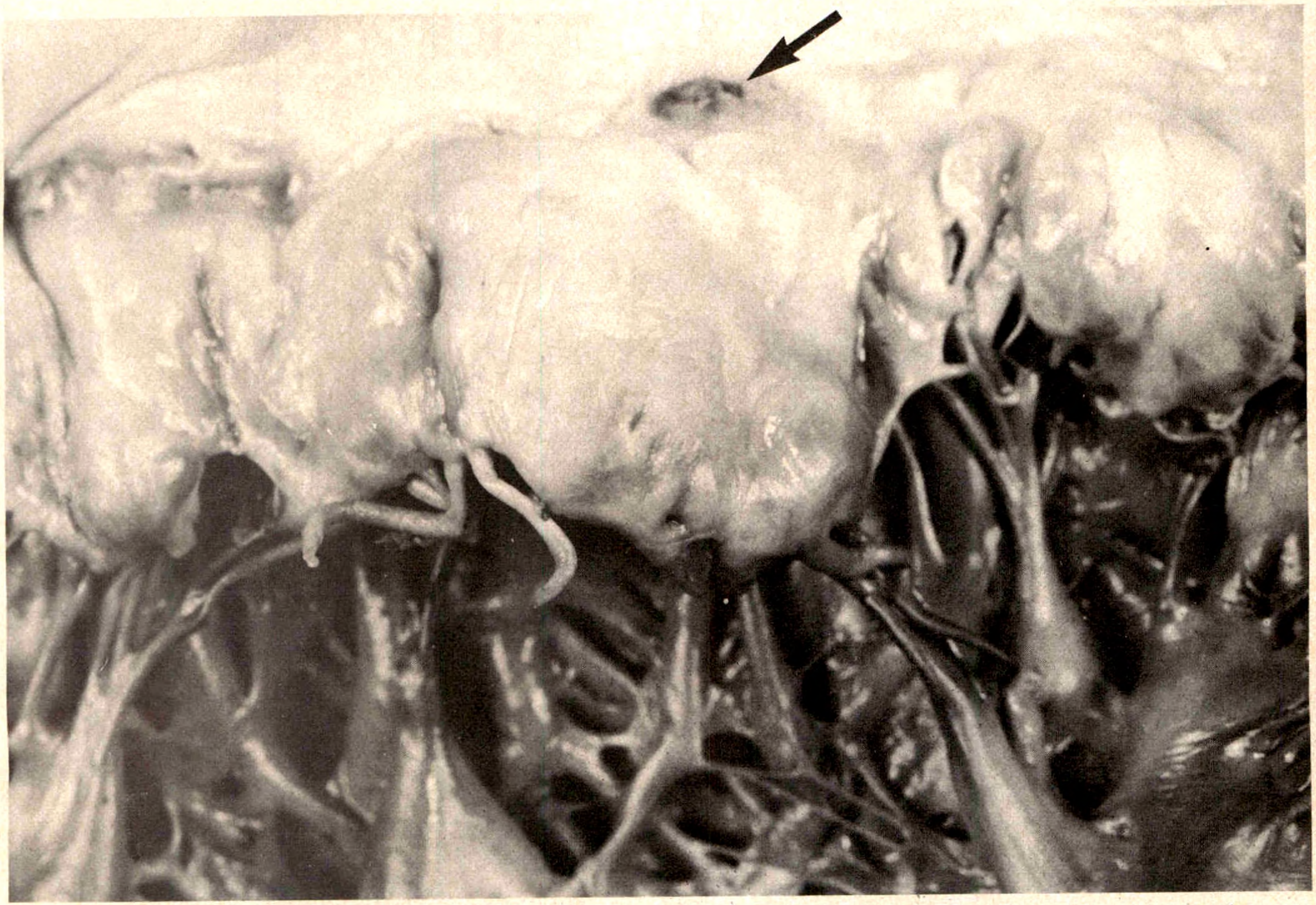

Fig 2.—Postmortem specimen indicates myxomatous valve degeneration, changes in chordae tendinae, and small area of premortem thrombotic material attached to roughened area at valve insertion (arrow) (from Silver[18]).

In September 1975, two abrupt episodes of right face, arm, and leg weakness occurred on arising, associated with an awareness of a pounding heart that lasted less than an hour. This heart pounding had been recurring every one to two weeks for about 15 years and had occurred twice on the day of the recurrent paralytic episode in 1975. She could not date an episode specifically to her first stroke. The physical findings were those of minimal right-sided weakness and an apical systolic murmur with midaccentuation to late accentuation. An echocardiogram was suggestive of a PMV. Cardiac monitoring indicated a sinus rhythm throughout the 24-hour period, but the rate varied from 75 to 140 beats per minute, with occasional atrial premature beats. Angiocardiography showed normal coronary arteries and a PMV. The carotid artery studies were repeated and reconfirmed persistent occlusion of the branch of the middle cerebral artery. All other arteries were normal.

Case 5.—A 38-year-old woman, in July 1972, had three episodes of right-sided numbness, weakness, and aphasia, lasting one to five hours. Cerebral angiography showed normal intracranial and extracranial arteries, except for a right pericallosal aneurysm. Although inappropriate to her symptoms, the unruptured aneurysm was clipped because of its size. In the succeeding year, three severe bouts associated with global weakness, sweating, and pallor came on suddenly and subsided slowly. Many bouts of palpitations were reported. In August 1973, she had a four-hour attack of left-sided weakness and dysarthria, with complete recovery. Repeat cerebral angiography was normal. Physical examination revealed two midsystolic clicks, 24-hour monitoring periods of sinus tachycardia, and frequent junctional premature beats, while echocardiography and left ventricular angiocardiography indicated a PMV.

Case 6.—A 39-year-old woman, in July 1972, experienced the sudden onset of left arm and leg paresis that cleared completely in several days. Cerebral angiography was normal. A severe left hemiplegia in September 1973 left some residua three months later. Cerebral angiography showed normal arteries, but a brain scan suggested a wedge infarct in the right hemisphere. Episodic attacks of palpitations lasting 15 minutes had occurred for 18 months, with associated light-headedness and atypical chest pain described as indigestion. These attacks could be aborted by Valsalva maneuvers. Twenty-four-hour monitoring revealed one to two junctional extrasystoles per minute. Cardiac catheterization and echocardiography indicated a PMV.

Case 7.—A 39-year-old man, developed a right hemiparesis and slurred speech on awakening in April 1974. Several weeks later, he had recovered except for slightly increased right-sided reflexes. Cerebral angiography was normal, and the brain scan indicated a wedge-shaped lesion in the left middle cerebral artery territory. There were no cardiac symptoms, but there was an apical systolic murmur. Twenty-four-hour monitoring indicated frequent premature ventricular contractions (PVCs). Although the echocardiogram was interpreted as being normal, cardiac catheterization displayed a PMV.

Case 8.—A 43-year-old man, in January

1974, experienced right-sided numbness and a dead feeling on the left side of his face, persisting two to three days. Findings from physical examination were normal. Left carotid and vertebral angiograms were normal. He had had occasional retrosternal atypical chest pain for eight years, and physical examination revealed a faint midsystolic click. Twenty-four-hour monitoring was normal. Cardiac catheterization and echocardiography showed a PMV.

Case 9.—A 47-year-old man, in 1970, had six days of aphasia, with complete recovery. In May 1971, he had right arm weakness for 24 hours, and, in September 1971, an attack of left hemiparesis and slurred speech for three weeks. His right common carotid angiogram was normal, but, unfortunately, the left carotid artery became occluded by a subintimal injection. In the summer of 1972, a left homonymous hemianopsia developed and lasted several hours. In September 1973, he had right arm weakness and aphasia for five minutes. Physical examination at that time showed no neurological abnormalities; a midsystolic flow murmur was heard, but there were no clicks. On 24-hour monitoring, four to five seconds of asymptomatic ventricular tachycardia was detected. Cardiac catheterization and echocardiogram indicated a PMV. Repeat cerebral angiography was unchanged.

He died suddenly in March 1975. It was assumed that he had suffered a ventricular dysrhythmia and cardiac arrest.

Case 10.—A 46-year-old man, in 1974, had eight to ten transient episodes of left hand and forearm numbness and occasional hand clumsiness lasting a few minutes. Two additional episodes of right leg numbness and weakness lasting up to half an hour led to investigation in September 1974. There had been occasional chest pain, often occurring at rest, but no history of palpitations. Examination indicated no neurological findings, but there was a pansystolic murmur and an S-4 heart sound. Resting ECG was normal, whereas 24-hour monitoring revealed paroxysmal atrial fibrillation. Cardiac catheterization and echocardiography displayed a PMV.

Case 11.—A 48-year-old woman, in June 1974, suddenly experienced a left hemiplegia, without headache. Angiography showed a right middle cerebral artery aneurysm and normal carotid arteries. Her spinal fluid was clear. Because of its size, the unruptured aneurysm was clipped. Postoperatively, she developed a severe left hemiplegia, and repeat angiography indicated massive cerebral edema of the left hemisphere and the appearance of arterial spasm. She made a complete recovery. In February 1975, she again developed a left hemiparesis, with severe motor and minimal sensory loss of which some residual signs persisted after nine months. Repeat cerebral angiograms were normal.

She had had a bout of severe chest pain three years prior to admission, but no other cardiac symptoms. There was an apical systolic murmur. Her resting ECG indicated left bundle branch block, and 72-hour monitoring was otherwise normal. Cardiac catheterization and echocardiography showed a PMV.

Case 12.—A 67-year-old man experienced sudden loss of vision in his right fields. He had a history of six bouts of slurred speech in the previous year. Examination showed a right homonymous hemianopsia, but no other neurological signs. Four-vessel cerebral angiography indicated an occluded right posterior cerebral artery and no other abnormalities. For four years, he had had palpitations, often nocturnal, lasting from a few minutes to 1½ hours. He had no cardiac findings. His resting ECG was normal, whereas his 24-hour cardiac monitoring indicated paroxysmal atrial fibrillation. Cardiac catheterization and echocardiography revealed a PMV.

GENERAL AND CARDIAC FEATURES OF THE CASES

Incidence

During the four years in which these 12 cases were studied, a total of 215 patients were proved by angiocardiography to have PMV. During the same period, we entered 154 patients with TIA and nonprogressing stroke and with clinical evidence of arterial disease into our platelet-inhibiting drug trial.

Seven patients with PMV were men and five were women, ranging in age from 18 to 67 years, with an average of 38 years. One of the female patients was taking an oral contraceptive at the time of her first symptoms, but when they recurred two years later she had not taken this treatment for two years. The other women had never taken oral contraceptives. None had histories suggestive of hemiplegic migraine. None had hypertension.

Cardiac Symptoms, Signs, and Investigation

Four of these patients had periodic bouts of chest pain. Five patients gave a history of palpitations. Two reported significant light-headedness, faintness, sweating, and pallor in conjunction with the other cardiac symptoms. Five patients had no cardiac complaints.

On examination, three patients were found to have midsystolic clicks, nine to have midsystolic, late systolic, or pansystolic murmurs at the apex; two had both a systolic murmur and midsystolic click or clicks, and two had normal results from cardiac examination.

The echocardiogram indicated the presence of PMV in eight patients and was normal in four. All patients had 24- to 72-hour cardiac monitoring: three patients had paroxysms of atrial fibrillation, one, who died suddenly two years later, had a burst of ventricular tachycardia, and one patient exhibited intraventricular conduction delay with a left posterior hemiblock. Paroxysms of sinus tachycardia were detected three times; in one patient with frequent junctional extrasystoles as well. One had frequent junctional extrasystoles alone. The rest had no abnormalities or simply frequent PVCs.

All of the patients had features on left ventricular angiography that were typical of PMV. The degree of prolapse was determined by examining the mitral valve closure line in the right anterior oblique projection (Fig 1).

NEUROLOGICAL ABNORMALITIES

None of these patients were thought to have PMV prior to the onset of the neurological symptoms. The neurological picture was characterized by multiple attacks in 8 and single attacks in 4 of the 12 patients.

The recurrent episodes were generally separated by many months or several years, but in some they were more frequent and closer together. The more frequent episodes were typical of the abrupt onset of TIA with complete early resolution. The single events or those separated by several months or years tended to be associated with more prolonged and occasionally persistent disability.

The attacks consisted of the onset of transient hemiparesis or major stroke in 9 of the 12 patients, with unilateral sensory loss in 4, dysarthria in 3, aphasia in 3, hemianopsia in 3, and a unilateral vestibular and auditory function loss in 1 patient. The events involved both hemispheres on separate occasions in three of the patients, were in carotid artery territory in ten of the patients, and in vertebral-basilar territory in two.

The appropriate cerebral arteries were visualized in all but patient 3. Six patients had repeat angiography one or more years later when recurrent events developed. All were free of recognizable arteriosclerotic disease in the neck and intracranial portions of the arteries. In four instances, an intracranial artery was occluded. In one (patient 12), an occluded posterior cerebral artery, appropriate to the symptoms of visual disturbances, was recognized. In this case, paroxysms of atrial fibrillation was identified on the monitor. In another (patient 2), a 19-year-old man with an abrupt stroke, an angiogram detected no disease in the major vessels, but evidence of occlusion of a branch of the appropriate middle cerebral artery. In a third (patient 4), a right hemiplegia was associated with a left middle cerebral branch occlusion, which was unchanged when a second episode occurred two years later. The fourth patient (patient 1) had a transient stroke at age 10 years, and a middle cerebral artery occlusion was identified. In the investigation of two further attacks nine years later, there was no residual occlusion nor new arterial lesion detectable.

COMMENT

Mitral valve prolapse is commonly characterized by chest pain, dyspnea, and cardiac arrhythmias of which paroxysmal atrial fibrillation is the most common. The condition may be totally asymptomatic. The usual physical findings of a midsystolic click or midsystolic to late systolic murmur or both are explained by the pathological changes in the mitral valve. Pathological study suggests that mucoid degeneration of various portions of the valve and chordal tissue results in stretching of these structures and consequent sagging of the involved tissue back into the left atrium during systole. Often this produces a minor, but at times severe, degree of mitral regurgitation. These myxomatous changes are of uncertain origin, but an abnormality of connective tissue, congenital or acquired, is thought to underlie the changes.[17] Other conditions, including rheumatic heart disease, trauma, and papillary muscle ischemic change, may be responsible for prolapse in a few instances.

Microscopically, the dense collagen of the valve cusp and of the chordae tendinae is replaced by a loose metachromatically staining myxomatous tissue. The surrounding endocardium is the site of increased fibroelastic tissue. The valve, surrounding endocardium, and chordae are less resistant to normal variations in intraventricular pressures and allow the prolapse to occur.

In a review of 35 postmortem cases, Pomerance[17] has illustrated tearing in the endocardium overlying the myxomatously degenerate valve, and in ten of these cases he described adherent fibrin and red blood cells. This "fibrinous endocarditis" was attributed to the loss of endothelial continuity and rupture of subendothelial connective tissue due to abrupt changes in tension. Two patients in his series had bacterial endocarditis. R. O. Heimbecker, MD, FRCP(C) (oral communication, June 1975), operating to replace a regurgitating mitral valve in this condition, has observed a small thrombus lying on the valve near its attachment. Silver[18] has illustrated a roughening of such a valvular lesion with adherent thrombus material (Fig 2) in a patient with no history of neurological complications.

The initial discovery of PMV and its detection in any given patient depend on the recent perfection of echocardiography and cineangiocardiography. The full significance of PMV is still under surveillance, and the full spectrum of the clinical presentation has not been established. Nevertheless, the occurrence of typical cardiac findings of PMV in 12 patients with significant cerebral ischemic events, without arterial disease, hematological disorder, or other heart disease, is difficult to dismiss as coincidence.

Important differences exist between these PMV cases and the series of patients studied by us with ischemic cerebral events judged to have been due to artery-to-artery emboli. The majority (89.3%) of the TIA treatment-trial series had recognizable angiographic changes compatible with atheromatous disease. None of the PMV patients had angiographic evidence of arteriosclerotic disease of the intracranial or extracranial cerebral arteries. The average age in the PMV group was 38 years compared with 62 years in the other series. Hypertension was absent from this group of 12 patients, while it was present at the time of recognition of the arterial disease in the larger series in 36% of the patients.

Hemodynamic mechanisms related to arrhythmia or emboli of cardiac origin exist as possibilities to explain the recurrent events in these PMV cases. Lacking pathological studies, our evidence is indirect, but it favors the fact that the process of thrombosis is involved, with resultant embolism from the heart. The focal nature of the neurological events, the involvement of both hemispheres at different times in 3 of the 12 patients, coupled with the four angiographic pictures of occluded intracranial arteries despite normal extracranial arteries all favor the embolic explanation. Pathological changes on the margin of the prolapsed valve, as described by Pomerance[17] and by Silver[18] (Fig 2) may initiate platelet adherence and aggregation, and a platelet-fibrin thrombus eventually may become detached.

Neurological symptoms secondary to cardiac arrhythmias are usually diffuse and related to low perfusion states.[19-21] Even with cerebral vascular disease, transient hypotension rarely produces or reproduces focal ischemic symptoms.[22] If the paroxysmal cardiac arrhythmias play any role in the development of focal cerebral symptoms, it could be by enhancing the tendency for thrombogenesis to occur on a diseased valve during an impaired state of cardiac function.

A review of the extensive literature on the subject of PMV has revealed only one other case report where this valvular lesion was associated with what could have been cerebral embolic episodes, other than those complicated by subacute bacterial endocarditis. Barlow and Bosman[15] reported a case in a woman afflicted with a transient left arm weakness at age 23 years. Thirty years later, she had a bout of chest pain, with sweating, breathlessness, and a further transient episode of left hemiparesis. Left ventricular cardiography and angiocardiography confirmed a posterior leaflet prolapse.

Therapy for these PMV patients will include antiarrhythmic agents, possibly anticoagulants, and, if the present cooperative studies now in progress confirm their efficacy, drugs that interfere with platelet function. In the meantime, the recognition of an association between cerebral ischemic episodes and PMVs reemphasizes the importance of careful cardiac examination and cardiac monitoring in patients with TIAs or partial nonprogressive strokes. This would appear to be of particular importance when the patients are in the younger age group, and there is normal cerebral angiography.

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Medullary Actions of Tetanus Toxin

An Electrophysiological Study in Man

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• Brain-stem reflexes have been studied in four patients with generalized tetanus. Inhibitory cutaneous reflexes were abolished or severely depressed. The same held true, to a lesser degree, for excitatory cutaneous reflexes with long polysynaptic pathways. Proprioceptive reflexes behaved variably. The observations are discussed in regard to the possible sources of enhanced motoneuronal activity in tetanus. It is concluded that, besides depression of inhibitory synapses on motoneurons, interneuronal damage may contribute to the tetanus symptomatology.

(*Arch Neurol* 33:783-785, 1976)

Electrophysiological investigations studying the medullary actions of tetanus toxin in cats[1-3] have stressed depression of synaptic inhibition as the source of tetanic motoneuron hyperexcitability. Struppler et al[4] confirmed this finding in man by showing a reduction of inhibitory reflexes in cases of localized and generalized tetanus. The present work further analyzes the possible sources of enhanced motoneuronal activity in tetanus patients by studying inhibitory as well as excitatory reflexes in the cranial musculature.

SUBJECTS AND METHODS

Ten normal control subjects of either sex and four men with generalized tetanus have been studied. During examination, the subjects reclined in bed. Mechanical stimuli were delivered by means of an electrodynamic type force generator to which an impedance head was attached (linear displacement, 1 to 3 mm; circular contact surface, 1.5 cm in diameter). The duration of the mechanical stimuli was 5 msec. Their intensity was adjustable from 0.01 newton to 10 newton, with steps of 0.01 newton. It was assessed by connecting the impedance head with an accelerometer preamplifier and measuring amplifier. Electrical stimuli were applied with a bipolar skin electrode (interelectrode distance, 2 cm). A constant current stimulator was used, delivering rectangular shocks of 0.5 msec in duration and 1 to 15 mamp in intensity at a frequency always kept below one cycle per three seconds.

Reflex responses were picked up from the masseter, orbicularis oris, and orbicularis oculi muscles by means of two cutaneous silver disk electrodes (0.7 cm in diameter) placed 3 cm apart. After amplification, the muscular responses were displayed on the cathode ray oscilloscope of an electromyographic apparatus and filmed on direct print paper.

In each subject, five brain-stem reflexes were studied:

(1) The *myotatic masseter reflex*,[5] or jaw jerk, was elicited by a downward tap to the chin. The recording electrodes were located over the masseter muscle, the reference electrode being placed at the level of the muscle tendon.

(2) The proprioceptive *masseteric silent period*[6,7] was studied after inducing on a background of spontaneous or voluntary electromyographic (EMG) activity a twitch contraction of the masseter muscle, either by myotatic reflex activation or by direct electrical muscle stimulation.

(3) The crossed *exteroceptive masseter inhibition*[6,8,9] was obtained on a background of spontaneous or voluntary EMG activity by electrical stimulation of the ipsilateral or contralateral labial mucosa.

(4) The *lip-tap reflex*[10] was induced in

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the orbicularis oris muscle by applying single, short mechanical pulses to the lips. The recording electrodes were placed over the orbicularis oris muscle near the corner of the mouth.

(5) The short- and long-latency *blink reflex* components[10-12] were analyzed after delivering single electrical pulses to the supraorbital skin. The recording electrodes were placed over the orbicularis oculi muscle at the level of the inferior eyelid margin.

RESULTS

Control Subjects

The ten normal subjects were between 22 and 60 years old. Control values for the several tested brainstem reflexes were obtained for the reflex threshold and on the reflex amplitude or duration. No statistical analysis was performed.

It has been reported previously that the normal human jaw jerk occurs after a latency of approximately 7 msec, and has a central relay time that strongly suggests a monosynaptic reflex.[5] In the present study, the jaw jerk was recorded as a biphasic summation potential whose peak-to-peak amplitude varied from 0.2 to 2.5 mV. Its threshold ranged from 0.7 to 1 newton chin tap intensity. The masseteric silent period had a duration of 20 to 100 msec, depending on the strength of the foregoing contraction. It was elicited by a threshold electrical stimulus of 5 to 7 mamp, just sufficient to induce a brief contraction of the masseter muscle. The exteroceptive suppression of voluntary masseter activity is known to contain an early and a late component (R_1 and R_2 inhibitory masseter, respectively), whose respective latencies are in the range of 10 to 15 msec and 30 to 60 msec, respectively.[6,9,13,14] On electrical stimulation of the labial mucosa in the control subjects, their threshold intensity varied from 3 to 4 mamp, being often slightly lower for the early component. The tap-induced lip reflex also contains an early and a late component.[15] The reflex is difficult to elicit at rest, and is more prominent when evoked on a background of slight voluntary activity.[14] In the control subjects, both lip reflex components (R_1 and R_2 lip-tap) were induced at much the same threshold intensity (0.2 to 0.3 newton) and had an amplitude ranging between 0.2 and 2 mV. The early and the late blink-reflex components (R_1 and R_2 blink) showed an amplitude of between 0.2 and 1.5 mV. They were elicited at approximately the same threshold intensity (3 to 5 mamp).

Brain Stem Reflexes in
Four Patients With
Generalized Tetanus

Reflex	Patient* 1	2	3	4
Jaw jerk	+↑	+	+	+
Silent period masseter	+↓	+	+↓	+
Inhibitory masseter				
R_1†	—	+↓	—	—
R_2†	—	—	—	—
Lip-tap				
R_1	+↑	+	+↑	+↑
R_2	—	—	+	+↓
Blink				
R_1	+↑	+	+↑	+
R_2	+↓	+↓	+	+↓

* + indicates normal; +↑, potentiated; +↓, depressed; and —, abolished.

†R_1 indicates early component; R_2, late component.

Patients

The four tetanus patients were conscious during examination. They had typical histories and symptoms, with trismus and severe rigidity in the extremity muscles. Case 1 also had marked hypertonia of the facial muscles, causing narrowing of the palpebral fissure and mild retraction of the corner of the mouth. In all the patients, the EMG examination of the masseter, orbicularis oris, and orbicularis oculi muscles revealed a spontaneous tonic activity of motor units pulsating at frequencies of between 10 and 40 cps. Three patients recovered after treatment. One (case 1) died from pneumonia. In each tetanus patient, the threshold, amplitude, and duration of the different investigated brain stem reflexes were analyzed and compared with the control values. The results are summarized in the Table.

Case 1.—A 26-year-old man was examined on the seventh day of tetanus symptoms. The jaw jerk was hyperactive. It was elicitable by light chin taps of 0.5 newton intensity and had a maximum peak-to-peak amplitude of about 6 mV. The subsequent silent period was brief (about 20 msec duration). When evoked by direct stimulation of the masseter muscle, it reached 40 msec in duration. The early and the late exteroceptive masseter inhibitions were abolished bilaterally. The early lip-tap reflex component was facilitated, being induced by taps of 0.1 newton in intensity and reaching an amplitude of 4 mV on stronger tapping. It was often followed by a transient pause in the orbicularis oris activity, lasting 10 to 20 msec. The late lip-tap reflex component was abolished. The two blink reflex components showed a marked difference in threshold: the early component had a low threshold (3 mamp) while the late component was elicited at a threshold intensity of about 10 mamp. The maximal amplitude was 2 mV for the early and 0.4 mV for the late component.

Case 2.—A 48-year-old man was examined on the tenth day of tetanus. The jaw jerk was normal and followed by a silent period lasting 30 to 50 msec. Direct electrical stimulation of the masseter muscle evoked a silent period of 60 msec. The short-latency exteroceptive masseter inhibition had an increased threshold intensity of 8 mamp. The long-latency exteroceptive masseter inhibition was abolished, as was the late lip-tap reflex component. By contrast, the early lip-tap reflex component was easily evoked on the background of spontaneous tonic orbicularis oris activity, by taps of 0.2 newton. It reached an amplitude of 2 mV. The first blink reflex component was normal, but often followed by a short pause of 10 to 15 msec in the spontaneous orbicularis oculi activity. The second blink reflex component had an increase in threshold, requiring a stimulation intensity at or above 9 mamp. Its amplitude remained within normal limits.

Case 3.—A 59-year-old man was examined on the ninth day of tetanus. The jaw jerk was potentiated, exhibiting a maximal amplitude of 5.5 mV, with a threshold of 0.6 newton. No subsequent silent period was observed. On electrical stimulation of the masseter muscle, the silent period never lasted more than 30 msec. Both the short- and the long-latency exteroceptive masseter inhibitions were abolished. The lip-tap reflex and the blink reflex components behaved similarly: their early component was potentiated, reaching amplitudes of 3 to 4 mV, while their late component remained within physiological limits. The reflex thresholds were normal.

Case 4.—A 53-year-old man was examined on the 12th day of tetanus. The jaw jerk and the masseter silent period were normal. The short- and long-latency exteroceptive masseter inhibitions were abolished. The early lip-tap reflex was facilitated: it was elicited at a threshold intensity of 0.2 newton and showed a maximal amplitude of 4.5 mV. The late lip-tap reflex was obtained at an increased threshold intensity of 0.8 newton, and had a low amplitude of about 0.5 mV. The early blink reflex component was normal, while the late blink reflex component had an increased threshold of 7 mamp.

COMMENT

In experimental animals, at least three actions have been attributed to tetanus toxin at the medullary level: (1) depression of inhibitory synapses on motoneurons,[1-3] (2) destruction of interneurons,[16] and (3) damage to motoneurons.[17] Although all these effects could theoretically produce motoneuronal hyperexcitability, disinhibition is most commonly accepted as the source of tetanic rigidity. The present observations are in agreement with this conclusion, confirming former EMG studies in man.[4] Both short- and long-latency inhibitory cutaneous reflexes in jaw-closing musculature were abolished or severely depressed in the tested patients. The results suggest, however, that, at least at the bulbar level, a disturbance in synaptic inhibition is not the sole factor involved in tetanus. Indeed, irrespective of their excitatory or inhibitory character, all late exteroceptive cranial reflex components were usually depressed, while short-latency excitatory reflexes were mostly enhanced. While the latter finding can be explained by the motoneuron hyperexcitability, the selective impairment of reflexes with long polysynaptic pathways supports the assumption of interneuronal dysfunction; interneuronal damage is well known as a cause of rigidity.[18]

Contrasting with the exteroceptive inhibitory reflexes, the proprioceptive masseteric silent period was never abolished in the tetanus patients. This likely results from its partial generation by motoneuronal disfacilitation.[6] In two patients, the jaw jerk and the proprioceptive masseteric silent period were normal. Two other patients had a marked potentiation of the jaw jerk, which coincided with a depression of the silent period. Instead of resulting from defective inhibitory synapses on α-motoneurons, the latter could be related to γ-motoneuron hyperactivity. If so, the behavior of proprioceptive reflexes in tetanus patients would depend on whether motoneuronal hyperexcitability is restricted to the alpha pool or involves both the alpha and the gamma pool. This could be an important factor in determining the severity of tetanic rigidity.

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Case Report

Postradiation Motor Neuron Syndrome

Carl H. Sadowsky, MD; Ernest Sachs, Jr, MD; José Ochoa, MD, PhD

• **We report an unusual case of selective lower motor neuron syndrome (MNS) complicating whole neuraxis radiation therapy. Only three well-documented similar cases have been found in a thorough review of the literature. The syndrome has a stereotyped time course and is self-limited. We discuss here possible pathogenetic mechanisms and their relationship to motor neuron disease.**

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Four types of radiation damage to the spinal cord have been recognized,[1] the rarest being lower motor neuron syndrome (MNS), presumably due to damage to anterior horn cells of the spinal cord. A recent example prompted review of possible pathogenetic mechanisms and their relationship to motor neuron disease (MND).

REPORT OF A CASE

A 15-year-old girl with a four-month history of frontal headache, vomiting, and diplopia was seen on June 7, 1973, as an outpatient at the Dartmouth-Hitchcock Medical Center. Findings on physical examination were as follows: bilateral 4 to 5 diopters of papilledema, vertical nystagmus, left sixth nerve paresis, dysmetria and past pointing of the left hand, and ataxia of gait. Brain scan showed increased uptake in the midline inferior to the torcular. Angiography demonstrated hydrocephalus and a left cerebellar mass high under the tentorium.

On June 11, a solid tumor (histologically malignant medulloblastoma) was removed from the vermis.

Postoperatively, the patient was treated (June 20 to July 25, 1973) with a course of cobalt 60 radiation to the skull (4,000 rads centrally), and a betatron-electron beam course of radiation to the spine. Using a scanning technique, a dose of 3,800 rads was delivered (July 18 to Aug 17) to the entire spine (4,763 rads at the surface) with fields 6 cm wide, scanning length 53.5 cm, and field length 3 cm. Chemotherapy was never administered.

When seen 11 months after radiation she complained of progressive difficulty in walking due to weakness of leg muscles for the past three months. She denied involvement of the arms, sensory symptoms, pain, or sphincter disorder. On examination she had definite weakness and muscle wasting of the lower limbs, worse distally. Light touch, pinprick, vibration, and position sense and two-point discrimination thresholds were entirely normal. Ankle jerks were absent, but all other deep tendon reflexes were 1+. Plantar responses were flexor. Spontaneous sweating of the feet was present.

Electrophysiological studies revealed normal motor conduction velocity and sural nerve action potentials, with bilateral advanced denervation of the extensor digitorum brevis, tibialis anterior, gastrocnemius, and vastus medialis muscles in order of severity.

Cerebrospinal fluid cytologic findings were normal (two lymphocytes, one large mononuclear cell, and 111 RBCs per cubic millimeter); protein concentration was 200 mg/100 ml and a myelogram was normal. Other investigations included a normal blood cell count, B_{12} level, and sedimentation rate.

On neurological evaluation one month later the patient was just able to stand aided by a cane. Flaccid weakness and atrophy of foot intrinsics and peroneal muscles was obvious. Sensory examination gave normal findings. Ankle jerks were absent. The CSF protein level was 118 mg/100 ml and cytologic results were normal. Follow-up electromyography of leg muscles was unchanged, and EMG and results of nerve conduction studies in upper limbs were normal.

A right ascending lateral popliteal nerve action potential was normal one year after radiation (Aug 13, 1974).

No new symptoms have developed and the patient's previous deficits have remained unchanged. She has consistently denied sensory symptoms.

COMMENT

This case seems identical in its clinical manifestations and evolution to the three cases reported by Greenfield and Stark.[2] Thus, all four cases have consisted of a selective lower motor neuron disease confined to lower limb muscles, starting three to eight months after radiation of the spinal axis. All have followed a subacute and progressive, self-limited course. A relatively large series of cases presumed to belong to this category was reported in 1969.[3] No detailed clinical information was provided; it is difficult, therefore, to subject that report to comparison.

It is unlikely that the clinical manifestations in our patient might have been the consequence of a recurrence of the medulloblastoma, with seeding of the subarachnoid space, as the picture progressed without involvement of sensory or autonomic function, without a cellular reaction in the CSF (on two occasions), and without development of pain. Further confidence was given by a normal myelogram and by the self-limited course of the process as assessed 16 months after the peak of weakness.

From clinical and electrophysiological data it seems clear that the disease process is a result of selective injury to the lower motor neuron. The possibility of subclinical damage to the central branch of primary sensory neurons or the peripheral branch of the small dorsal root ganglia cells

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cannot be ruled out.

The primary site of injury within the lower motor neuron cannot be established with certainty. If ionizing radiation had caused the syndrome through direct damage of nerve roots, one would have expected combined motor and sensory manifestations.[4] In the cases under discussion there was complete sparing of all clinical sensory modalities. Hence, primary involvement of the anterior horn cells is most likely, and not only by exclusion. Studies on the rat sciatic nerve point out that the CNS is more sensitive to ionizing radiation than the nerve trunk.[5] Kristensson et al,[6] in a pathological analysis of five cases of delayed radiation lesions in man, demonstrated well-preserved spinal roots adjacent to markedly destructive lesions of the spinal cord. Further, there is good evidence to support susceptibility of anterior horn cells to ionizing radiation. Olkowski[7] reported a decrease in uptake by motor neurons of tritiated uridine in total-body radiated rats, suggesting decreased RNA synthesis in these cells. Thus, damage to anterior horn cells following radiation appears to be confirmed.

Selective damage to lumbosacral motor neurons is unsurprising in Greenfield and Stark's patients, who received focal radiation. However, our patient received whole neuraxis radiation. We have no way of advancing into the questions of radiation field overlap vs regional selective cell vulnerability.

Another puzzle is the rarity of this syndrome. At this stage one can only speculate: ionizing radiation may have activated a latent virus. This possibility can be entertained from evidence of herpes simplex virus activation after modification of physical variables (fever, ultraviolet radiation, surgery of the fifth cranial nerve in tic douleureux, etc). Extrapolation of an analogous mechanism for motor neuron disease has been disappointing. Indeed, evidence derived from morphological studies on neuronal inclusions in MND,[8] and from unsuccessful attempts at isolating and transferring virus in such a condition, has been inconclusive.[8,9] There are, however, fairly convincing documents on the development of a MND-like picture as a late sequel of poliovirus infection.[10] Thus, even though MND (Charcot disease) may be unrelated to viral infection, it is quite possible that motor neurons may be circumstantially involved in a progressive disease process caused by a virus. As to the possible effect of ionizing radiation itself as an effective trigger for viral activation, there is the precedent of the virus-induced thymic lymphoma in mice.[11] Following radiation this species develops a thymus neoplasm attributed to activation of a latent leukemia virus that can be isolated from the affected tissue. Altogether, it seems reasonable to regard virus activation as a viable hypothesis for postradiation MNS. Despite a negative history for poliomyelitis, this virus or other viruses cannot be excluded in the case we have described here.

A second alternative to account for such rare selective degeneration of motor neurons would be some metabolic deviation, of genetic origin, leading to an aberrant response to environmental influences. In the same way that, for example, individuals with xeroderma pigmentosum[12] have a special liability to light exposure, others may be particularly liable to ionizing radiation: this is certainly true at least for mice.[13]

Finally, it is also conceivable that radiation has ultimately caused selective motor neuron degeneration as a manifestation of ischemic cell damage, the one pathogenesis proposed by Greenfield and Stark.[2] Both the predilection of ionizing radiation injury for the vascular endothelium, and the occasional selective loss of motor neurons following ischemia, have been confirmed. Indeed, a fashionable explanation for radiation myelopathy is vascular injury.[14,15] Further, pathological and clinical studies on the effects of aortic clamping (in treatment of coarctation),[16] cardiac arrest,[17] dissecting aneurysm of the aorta, and atheromatous emboli to the spinal cord[18] have contributed convincing data on selective anterior horn cell degeneration following ischemia.

Although we can only contribute speculation on the question of the nature of cell damage in this syndrome, it seems likely that it results from damage to the motor neuron as opposed to the nerve or nerve roots.

Dr Marchant Tulloh gave helpful comments regarding the radiation scheme used in this case.

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Mercury Poisoning in a Dentist

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• We examined a dentist with chronic elemental mercury poisoning electrophysiologically. Motor conduction in the upper and lower limbs was normal. Sensory nerve action potentials in the ulnar and median nerves were normal, but could not be elicited in the superficial peroneal nerves. Conduction velocity of the sural nerves was normal, but the action potential amplitude was abnormal. Following treatment with penicillamine, sensory conductions in the lower limbs returned to normal.

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Although sensory impairment is considered to be one of the initial symptoms of organic mercury poisoning[1,2] and, possibly, may be the only presenting symptom,[3] there have been few electrophysiological studies of the peripheral nerves in these patients. A recent investigation[4] reported that, despite persistent clinical sensory deficit, both amplitude and velocity of the sensory nerve action potentials were normal, suggesting that the sensory impairment is due, primarily, to lesions of the central nervous system. Similarly, Von Burg and Rustam[5] did not find any abnormal motor and sensory conduction in patients exposed to methylmercury even though they found central lesions and myasthenic-like responses that suggested peripheral nerve involvement. They attributed the negative results to clinical improvement of the patients during the seven months that elapsed between examination and exposure. Since, to our knowledge, there have been no published results of electrophysiological studies of patients intoxicated with elemental mercury, we present a report of a patient with chronic elemental mercury poisoning and the apparent successful treatment with penicillamine.

REPORT OF A CASE

A 53-year-old male dentist noted in October 1973 that he felt like a "senile old man" after some years of emotional instability and depression. He was examined by an internist who could not find any physical abnormalities and advised psychiatric evaluation. The patient did see a psychiatrist and undertook a therapeutic program for about four months, without any changes in either physical or mental status. In November 1973, the patient noticed development of tingling and numbness of both feet that was exaggerated by walking even half a block. In March 1974, he returned to his internist for further labora-

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tory tests, and all results were reported as normal. Later that year, in May, he became subjectively aware of difficulty in differentiating between hot and cold while bathing; the "entire body" seemed to be involved. At that time, a question arose as to whether he had peripheral vascular disease, and he sought the advice of a friend (J.G.) who detected no evidence of peripheral vascular disease, but noted that there was diminished to absent vibration and position sense in both lower extremities. On the same day, he was seen by a consultant neurologist who found trace deep tendon reflexes in both lower extremities and confirmed absence of vibration sense below knees, bilaterally. Otherwise, the findings from neurological examination were normal. Electrodiagnostic studies led to a diagnosis of sensory polyneuropathy on the basis of abnormal sensory nerve action potentials in the lower extremities. One week after this study, he noticed the onset of similar complaints in the hands, and he began to drop instruments and other objects frequently. A search for toxic polyneuropathy was made, and only after detailed persistent questioning was a history of handling mercury in the preparation of amalgam for fillings revealed. Twenty-four-hour urinary mercury level was found to be abnormal. The patient was then removed from exposure for five weeks and treated with penicillamine, 250 mg given orally four times a day, until November 1974. Subsequently, there has been a slow but progressive improvement to normal physical as well as mental status of the patient to permit a return to full-time professional activity. The vibration sense, position sense, and deep tendon reflexes in the lower extremities have returned to normal. He is able to differentiate hot and cold, and he does not drop small objects.

RESULTS

All the electrodiagnostic studies were performed by the same investigator (K.I.). Latencies and motor conduction velocities measured in the median, ulnar, peroneal, and tibial nerves before and after treatment were normal. Similarly, latencies and amplitudes of the antidromic sensory nerve action potentials of the median and ulnar nerves were normal. A typical examination showed a latency and amplitude, when stimulation was applied to the wrist, of 3.5 msec and 19μV for the left median nerve and 2.5 msec and 34μV for the right ulnar nerve.

Mercury Concentration in Urine and Sensory Nerve Action Potentials

Date	Mercury in Urine, μg/Liter	Treatment	Superficial Peroneal			
			Left		Right	
			Amplitude, μV	Conduction Velocity, m/sec	Amplitude, μV	Conduction Velocity, m/sec
May 1974	...	...	NR*	NR	NR	NR
July	...	...	NR	NR	NR	NR
Sept						
16	33	...	...	...	...	...
20	40	...	...	...	...	...
22	...	Yes	...	...	...	...
23	18	Yes	...	...	...	...
24	26	Yes	...	...	...	...
25	21	Yes	...	...	...	...
26	...	No	...	...	...	...
Oct						
5	...	Yes	...	...	...	...
6	55	Yes	...	...	...	...
7	45	Yes	...	...	...	...
8	20	Yes	...	...	...	...
9	26	Yes	...	...	2.4†	39.2
10	48	Yes	...	...	...	...
11	60	Yes	...	...	...	...
14	34	Yes	...	...	...	...
19	31	Yes	...	...	...	...
23	40	Yes	...	...	...	...
30	26	Yes	...	...	...	...
Nov						
6	28	Yes	...	...	...	...
15	38	Yes	...	...	...	...
20	23	Yes	...	...	...	...
22	...	No	...	...	...	...
28	22	No	...	...	...	...
Dec 18	27	No	...	...	...	...
Jan 1975						
12	40	No	...	...	...	...
19	22	No	...	...	...	...
26	20	No	NR	NR	8.0	54.0
Feb 26	20	No	...	...	...	...
April 9	15	No	...	...	...	...
May 14	7	No	10.0	58.8	11.0	52.7
July 16	14	No	...	...	...	...
Sept 24	10	No	10.0	53.3	11.0	52.8

*No response.

†Obtained by electronic averaging.

Prior to medication, sensory nerve action potentials could not be elicited from the superficial peroneal nerves bilaterally, and the amplitude of the evoked potential from the sural nerves was lower than normal. In May 1974, conduction velocity and amplitude in the right sural nerve were 51.8 m/sec and 8μV, respectively. (In our laboratory, normal values for conduction velocity and amplitude of the sensory nerve fibers in the lower extremities are 47.0 m/sec [SD, 3.0] and 17.0μV [SD, 4.5], respectively.)

Starting in September 1974, mercury levels in the urine were monitored almost daily (Table). Prior to medication, the concentrations were 33μg and 40μg/liter, which are high values even for dental practitioners. About 10μg/liter is considered the upper limit for urinary mercury excretion of nonoccupationally exposed individuals[6]; whereas, a recent environmental study of mercury contamination in dental offices set 30μg/liter as the maximum acceptable limit for personnel employed in dentistry.[7] On Sept

22, 1974, the patient started a daily regimen of penicillamine. Since acute sensitivity reactions, such as fever, rashes, leukopenia, eosinophilia, and thrombocytopenia, have been reported with this drug, white and red blood cell counts were monitored during the course of the therapy. No untoward effects were noted.

During the course of treatment, mercury excretion increased, especially in October, reaching a peak of 60μg/liter. Sensory nerve action potentials could then be evoked in the right superficial peroneal nerve; however, the conduction velocity was slow, and the amplitude of the response was very low (Table). Penicillamine therapy was continued through Nov 20, 1974, at which time urinary excretion of mercury stabilized below the accepted limit (30μg/liter) for dentists.

In January 1975, normal latency and sensory conduction velocity were observed in the right superficial peroneal nerve; however, the amplitude of the evoked potential continued low, and the nerve on the left side was still nonresponsive. Repeat tests in May and September 1975 demonstrated normal sensory responses in both the right and left superficial peroneal nerves.

COMMENT

Dental office personnel may suffer either acute or chronic mercury intoxication mainly because of inhalation of mercury vapor while they prepare and handle dental amalgam.[8] The immediate vicinity of such handling operations as well as spilled mercury or improperly stored mercury-containing wastes are also sources of exposure. Since our patient was a dentist and subject to some degree of exposure to such mercury vapor, we consider this a case of elemental mercury poisoning.

This case demonstrates that elemental mercury intoxication can measurably alter conduction along the sensory nerve fibers. The peripheral nerves in the lower extremities appear to be most sensitive, especially the superficial peroneal, which was completely nonresponsive. Early involvement of the sensory nerve fibers in the lower limbs is not an unusual finding in polyneuropathy. The first signs of a polyneuropathy are most frequently elicited in the sensory fibers of the distal parts of the lower extremities,[8] while conduction velocities of motor fibers may be normal. DiBenedetto[8] found that, in patients with clinical symptoms of peripheral neuropathy, 82% of sensory nerve action potentials of the superficial peroneal nerve and 68% of the sural nerve responses were absent. There was no difficulty in evoking a good sensory response from normal adults, which is also true in our laboratory.

It is recommended that in suspected cases of chronic mercury poisoning, either organic or elemental, the superficial peroneal (sensory) and sural nerves be carefully examined electrophysiologically for evidence of neuropathy. In this patient, the efficacy of penicillamine in the treatment of elemental mercury intoxication is substantiated.[9,10]

This investigation was supported in part by a grant from the Muscular Dystrophy Associations of America.

Nonproprietary Name and Trademark of Drug

Penicillamine—*Cuprimine.*

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The Effect of Acidosis in Hypokalemic Periodic Paralysis

Maureen A. Jarrell; Melvin Greer, MD; Thomas H. Maren, MD

• Metabolic acidosis was produced in two patients with hypokalemic periodic paralysis by the administration of ammonium chloride over a period of three days. The challenging test of glucose and insulin produced a substantially smaller reduction of both serum potassium concentration and muscle strength than when the patients were tested in normal acid-base balance.

The findings agree with earlier work on acetazolamide, suggesting that metabolic acidosis provides protection against episodes of muscle weakness in periodic paralysis.

(*Arch Neurol* 33:791-793, 1976)

Acetazolamide has been effective in the treatment of the familial periodic paralyses. For the hypokalemic form of the disease, the mechanism appears to be protection against the fall in serum potassium level. Acetazolamide blunts the fall in serum potassium level precipitated by administration of glucose and insulin and reduces the induced paralysis.[1] As a result, we postulated that the metabolic acidosis produced by acetazolamide was the major factor in achieving the beneficial responses. This is in agreement with Viskoper et al,[2] who administered ammonium chloride intravenously and reported an improved electromyogram in a patient with hypokalemic periodic paralysis.

This report involves two previously studied patients[1] in whom ammonium chloride was used to show the effect of acidosis in protecting against weakness produced by the administration of glucose and insulin. Our findings confirm the original theory that the production of metabolic acidosis is the mechanism of action of acetazolamide in the treatment of hypokalemic periodic paralysis.

REPORT OF CASES

The two brothers involved in this study were described in our earlier article[1] as cases 1 and 2. The same numbers are used here. General physical and laboratory findings were normal in both unless noted.

CASE 1.–A 28-year-old man had taken acetazolamide intermittently since 1972. His weakness is generally mild. The drug decreased the duration, severity, and frequency of his episodes. He had not taken acetazolamide for several months prior to the present study. He was obese and had a mildly elevated blood pressure.

CASE 2.–A 32-year-old man, the brother of patient 1, was placed on a regimen of acetazolamide in 1972 and experienced a decrease in number, duration, and severity of attacks. With treatment, he still had episodes of mild weakness approximately once a month. After a complete description of the experimental procedure, the patient volunteered to terminate acetazolamide therapy two weeks prior to admission. Shortly thereafter, he developed bothersome but not incapacitating periods of muscle weakness.

METHODS

Blood samples and urine specimens were collected from the fasting patients in the mornings of days 1 and 2. On day 2, a four-hour glucose tolerance test was administered; serum potassium levels were monitored during this period. Following this procedure, the patients received 12 gm of ammonium chloride per day. Gelatin capsules containing 1 gm of ammonium chloride were given in 2-gm doses at noon, 4 PM, and 8 PM, and in 3-gm doses at midnight and 8 am. The 4-AM dose was omitted to avoid gastric upset. Patient 1 drank 100 ml of milk following each ammonium chloride administration. Venous blood pH, Pco_2, Po_2, and total CO_2 levels were determined daily.

Both patients were challenged with glucose (1.75 gm/kg orally as Glucola) and insulin (20 units subcutaneously) on the third day of ammonium chloride adminis-

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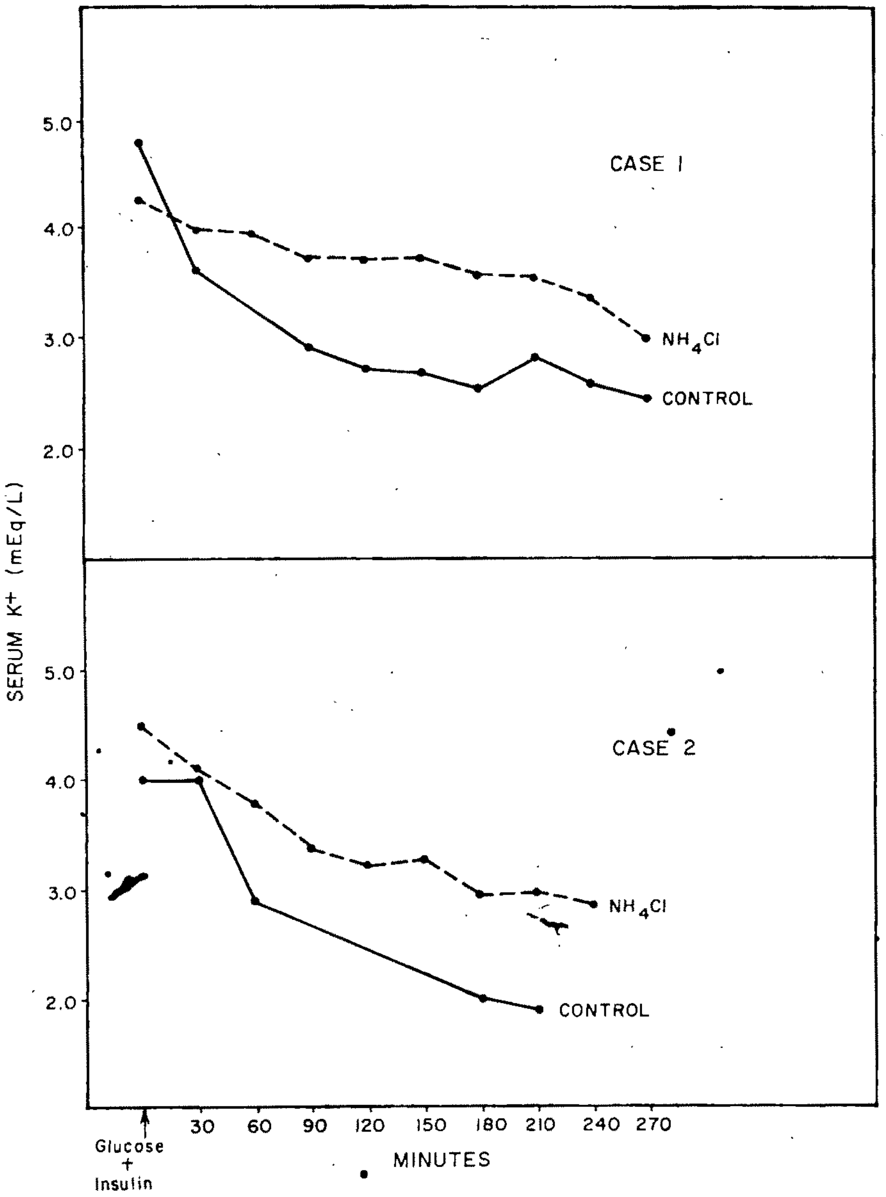
Acid-Base Values Following Oral Ammonium Chloride Administration to Two Patients

Hours After Initial Dose	Total NH_4Cl Given, gm	pH	Pco_2, mm Hg	Total CO_2, mM
Case 1				
Control	...	7.44	...	26
6	5	7.30	46	23
26.5	15	7.30	38	19
52.5	29	7.22	41	18
68	37	7.23	28	12
Case 2				
Control	...	7.45	...	28
6	5	7.32	37	20
26.5	15	7.34	32	18
52.5	29	7.28	37	18
68	37	7.26	27	13

Fig 1.—Modification by ammonium chloride of the hypokalemic effect of glucose-insulin in patients with hypokalemic paralysis.



tration. Venous blood samples were drawn every 30 minutes from a 19-gauge scalp vein needle, which was kept open by a slow, normal saline drip. Whole blood was analyzed for glucose, and serum for potassium, as in the previous study.[1] Electrocardiogram and muscle strength were monitored throughout the study.

RESULTS

Ammonium chloride treatment over a three-day period produced metabolic acidosis in both patients (Table). The patients suffered no gastric discomfort but mentioned an occasional, mild, esophageal burning at the time of ammonium chloride ingestion.

The glucose-insulin test produced no weakness in patient 1. Patient 2, who had the more severe disease, developed mild proximal weakness one hour after the administration of glucose-insulin. Right elbow flexor weakness was most prominent and may have been related to the indwelling venous line. Three hours after the test, only mild right elbow flexor weakness remained; this returned to normal in about five hours. In previous studies after the glucose-insulin test without other treatment, patient 1 had no weakness, but patient 2 showed severe muscle weakness, requiring oral administration of potassium.[1] The weakness appeared to be much milder following ammonium chloride pretreatment.

The serum potassium response to glucose and insulin was blunted by ammonium chloride acidosis (Fig 1). In that figure, the control data are from our earlier study on the same patients (Table 2 of reference 1). Figure 2 compares present results with acidosis caused by acetazolamide.[1] In case 1, ammonium chloride had a greater effect than acetazolamide; in case 2, less. Following ammonium chloride administration, the plasma bicarbonate concentration was much lower (13 mM) than in the acetazolamide experiment (22 mM). However, a tissue acidosis of respiratory origin in the acetazolamide experiment is not reflected in the measured acid-base chemistry.[3] This is discussed below.

Both patients were found to be diabetic during glucose tolerance testing. Following the administration of glucose alone, serum potassium concentrations decreased about 1 to 1.5 mM; this drop was less than that produced by glucose and insulin, usually 2 mM.

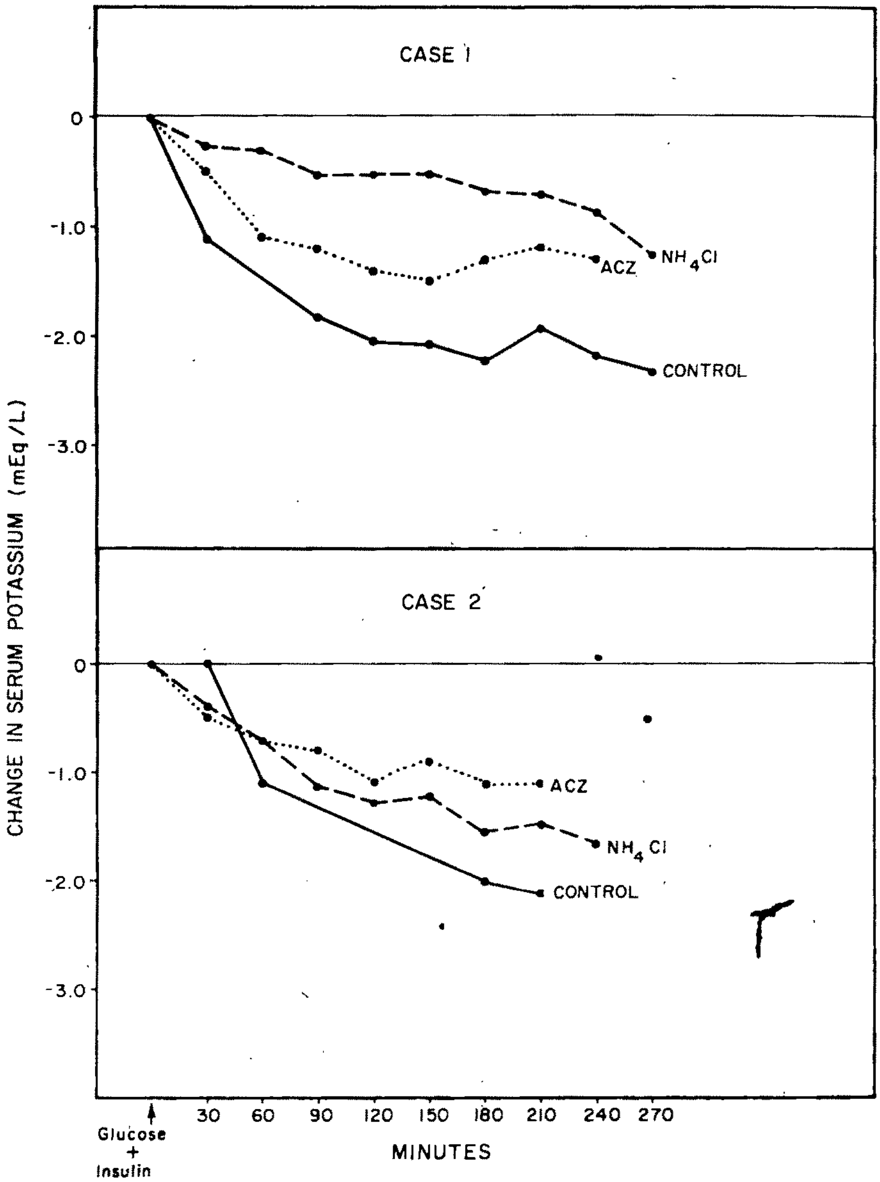
COMMENT

The present data confirm our inference that the mechanism of action of acetazolamide is through the induction of a metabolic acidosis rather than a direct effect on the muscle.[1] The metabolic acidosis engendered by acetazolamide is secondary to its renal effect in promoting bicarbonate loss. In patients with hypokalemic periodic paralysis treated successfully with acetazolamide, blood pH declines modestly to about 7.35.[1-4] But since the acidosis achieved by acetazolamide also has a respiratory component and a disequilibrium between H_2CO_2/CO_2 is created, the tissue P_{CO_2} is actually greater than indicated by plasma acid-base balance.[3] The effects observed are an extension of known physiological effects in the normal: in the acidotic dog, the usual hypokalemic effect of insulin is abolished.[5]

The effects of ammonium chloride have been shown to be similar to that of acetazolamide in blunting the effect of glucose-insulin on serum potassium concentrations by means of inducing an acidosis. The two agents reduce both the rate of potassium decrement and the total fall. Further studies are needed to show quantitative relations between plasma bicarbonate levels and the effect of either acetazolamide or ammonium chloride in blocking the glucose-insulin effect. The data do suggest, however, that in the control of these patients, attention might be given to the level of plasma bicarbonate achieved by acetazolamide. From these and other studies, it appears that, for maximum lowering of HCO_3^-, at least 250 mg every four to six hours should be given and that it may be wise to begin treatment with initial doses of 500 mg.

We have provided a model of the quantitative factors involved in the flux of potassium from serum to muscle and have shown how this flux may be increased in this disease. This calculation shows that an attack of hypokalemic periodic paralysis that reduces serum potassium from 4 to 2 mM involves an increase in potassium flux from serum to muscle of only about 1%.[1] Acidosis reduces or abolishes this pathological change and protects the patient from attack.

Fig 2.—Comparison of ammonium chloride and acetazolamide in protecting against hypokalemia following glucose-insulin in patients with hypokalemic paralysis. ACZ refers to earlier study with acetazolamide in same patients.[1]



This work was supported by grant GM 16934 from the National Institutes of Health. The studies were done in the Clinical Research Center of the University of Florida, Gainesville, supported by NIH RR-82-12.

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Letters and Clinical Notes

The editor will be pleased to receive correspondence of 250 words or less that pertains to material published in the ARCHIVES or to other matters of interest to its readers. Letters should be type-written double-spaced and should be clearly marked "For Publication." No more than 5 references are permitted and illustrations and tables are acceptable only when essential to the message.

Diphasic Response to Corticosteroids in Idiopathic Relapsing Polyneuropathy

Corticosteroid treatment has been associated with prolonged remissions in chronic idiopathic relapsing polyneuritis (IRP).[1-4] Recently, it has been noted that this response may require prolonged therapy,[2] but can be maintained with alternate-day corticosteroid administration.[3] Some authors have not noted a beneficial effect[5] or have noted a worsening with corticosteroid therapy.[4,6] The possibility that an initial worsening might precede improvement has not been considered.

We have treated a man with IRP whose initial response to corticosteroids was a dramatic worsening on each of four occasions. Although this response led to cessation of therapy on the first trials, eventual continuation of corticosteroids was associated with recovery from total quadriplegia and respirator dependence. A similar diphasic response was observed during subsequent reintroduction of therapy.

Report of a Case.—A 63-year-old man noted the onset of weakness and paresthesias of the hands in April 1972. Weakness progressed, and, by May 1972, he had severe generalized weakness with inability to raise his arms, walk, sit up from a supine position, or rise from a chair. He was areflexic and had slight sensory loss. Electromyography and a muscle biopsy specimen showed denervation, and repetitive nerve stimulation was normal. A sural nerve biopsy specimen showed loss of myelin and increased endoneural connective tissue without onion bulbs. No inflammation or edema was noted. Findings from metabolic and toxic studies were negative. Cerebrospinal fluid showed a persistently elevated protein level (75 mg to 233 mg/100 ml).

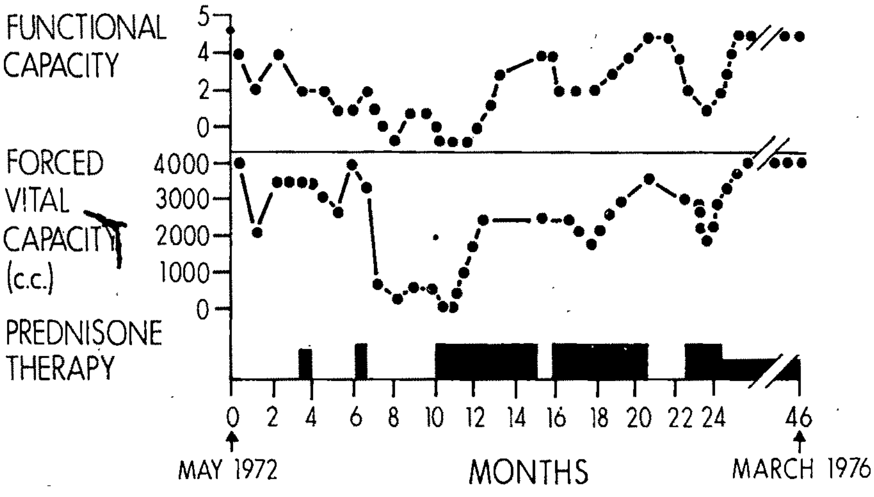
After admission, he improved and began walking, but then worsened and subsequently had multiple distinct exacerbations (Figure). He remained bedfast, and, in July 1972, prednisone treatment, 80 mg/day, was begun. Abrupt worsening occurred, leading to termination of therapy after 13 days. In October 1972, a second trial of prednisone was instituted. Abrupt deterioration in respiratory function occurred, and prednisone was discontinued after ten days. The patient subsequently required tracheostomy, feeding gastrostomy, and an indwelling catheter. A seven-week trial of azathioprine produced no improvement.

After five months of total respiratory support, a third trial of corticosteroids (prednisone, 120 mg given on alternate days) was administered. About three weeks after an initial worsening, improvement occurred, with return of respiratory function, swallowing, and bladder function. Over the next five months, the patient became ambulatory. Subsequent cessation of prednisone was associated with relapse. During reintroduction of alternate-day prednisone, vital capacity fell by 1,000 ml, and weakness worsened for three weeks. He again improved with maintenance therapy and over a 12-month period has returned to normal. Corticosteroids have been continued in tapering alternate-day dosage.

Comment.—It is possible that the four relapses in this patient during corticosteroid administration were a coincidence. It is clear, however, that corticosteroids either did not prevent acute worsening or were associated with its occurrence. Other authors have noted abrupt deterioration of function during corticosteroid treatment of IRP and discontinued therapy.[4,6] In several cases, corticosteroid therapy was not reintroduced despite an inexorable and ultimately fatal course. Although the basis for the deterioration of function in our patient is not known, an analogous situation appears to exist in myasthenia gravis where deterioration occurs early and is followed by improvement[7] that is often maintained with continued therapy.[8] Moreover, the recognition of the value of corticosteroids in myasthenia gravis was delayed because of this diphasic response.[9] While the basis for the deterioration seen in patients with myasthenia gravis is not known, an effect on the thymus or other lymphoid tissue has been postulated.[10] It is noteworthy that one reported patient with IRP who deteriorated during corticosteroid therapy subsequently proved to have lymphocytic infiltration of nerves.[6]

A recent, thorough review of chronic idiopathic polyradiculoneuropathy concluded that corticosteroids were not beneficial.[5] Since patients with a relapsing course were not distinguished from those with a chronic progressive neuropathy, a potentially treatable subgroup may have been obscured. Our patient was more severely afflicted and his response more favorable than most of the patients in this series Thus, it may be worthwhile to attempt treatment with corticosteroids in those patients with chronic idiopathic polyneuropathy and a *severe relapsing* course. The favorable results in our patient suggest that an initial adverse response to corticosteroids should not necessarily discourage further therapy.

Relapsing course of patient and response to the treatment. Several spontaneous relapses occurred and abrupt worsening followed corticosteroid therapy. Prolonged remission during maintained therapy. Functional capacity graded as 5, normal; 4, opposing resistance in all muscle groups; 3, all muscle groups full range of motion; 2, some muscle groups functional. 1, trace; 0, quadriplegia; —1, loss of sphincter function.



This investigation was supported in part by a grant from the Muscular Dystrophy Association.

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Paraparesis Secondary to Sodium Urate Deposits in the Ligamentum Flavum

Compression of the spinal cord or roots by sodium urate deposits has been demonstrated previously only twice.[1,2] In three other autopsy cases, sodium urate was deposited in tissues surrounding the spinal cord and cauda equina, including vertebral bodies and disks,[3] intervertebral facets,[4] and odontoid, atlas, and dura.[5]

Report of a Case.—We examined a 74-year-old man who had gout and hyperuricemia since 1964 (serum levels have varied from 7.1 to 10.6 mg/dl). For the two years preceding hospital admission, allopurinol, 400 mg/day, and colchicine, 1.0 mg/day, were prescribed, but probably not taken regularly. The patient noted severe, unrelenting pain radiating into both buttocks in February 1975. The pain was aggravated by sitting on a toilet seat, but not by Valsalva maneuvers. The pain gradually increased in intensity, and paresis of dorsi and plantar flexion of both feet developed in May 1975. A myelogram showed a complete block at the body of the fourth lumbar vertebra with posterior encroachment on the dural sac at the level of the lamina of L-4 (Fig 1). The cerebrospinal fluid protein level was 64 mg/dl. An electromyogram confirmed bilateral denervation potentials in distribution of the L-5 and S-1 nerve roots. On sensory examination, there was patchy diminution of touch, two-point discrimination, and pain in both legs. Vibration sense and position sense were decreased below the knees bilaterally. Motor examination revealed a patient unable to stand, with a distal paresis of both anterior and posterior tibial muscles. Straight leg raising produced a pain at 45° bilaterally. Deep tendon reflexes were normal and symmetrical except for absent ankle jerks; the plantar responses were flexor. Abdominal and cremasteric reflexes were present. Although the patient denied having bladder or bowel symptoms, a cystometrogram showed a flaccid bladder.

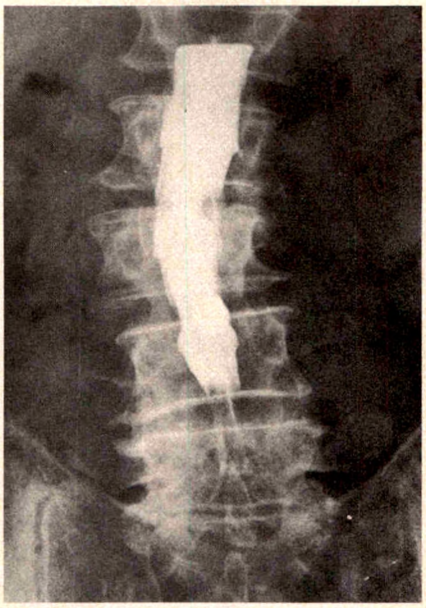

Fig 1.—Anteroposterior lumbar myelogram. Note complete block at inferior margin of L-4.

At laminectomy, the facets were noted to be considerably enlarged and abnormally white. The ligamentum flavum at both L-4 and L-5 was chalky white and greatly thickened. After resection of the abnormal ligamentum flavum, the dural sac became freely pulsatile, and the wound was closed. Immediately after surgery, the severe pain in the buttocks cleared. Two months later, the patient had regained full power in his legs.

The ligamentum flavum contained focal deposits of amorphous material and typical microscopic tophi composed of needle-shaped crystals with surrounding young fibroblasts intermixed with lymphocytes, plasma cells, and foreign body giant cells (Fig 2). Special stains[6] showed urate crystals in both the amorphous masses and the tophi.

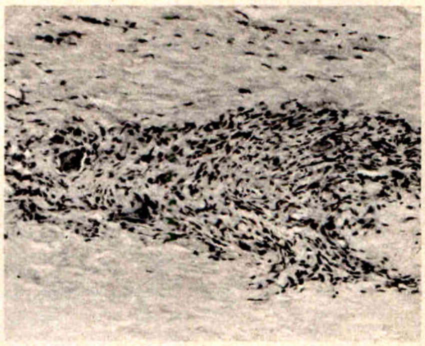

Fig 2.—Tophus in ligamentum flavum. Note foreign body giant cells, fibroblasts, and needle-like empty spaces where urate crystals have been removed (hematoxylin-eosin).

Comment.—Of the two cases of spinal cord compression previously reported, the deposits in the first case[1] were anterior to the dura and extended from the upper border of T-9 to the middle of T-11. The deposits in the second case[2] were in the ligamentum flavum at the level of L-3. The latter patient was paraparetic, but recovered after decompressive laminectomy.

In the patient reported by Kersley et al,[5] urate deposited in the axis and atlas resulted in subluxation of C-1 on C-2. At autopsy, deposits of urate were seen in the lateral masses of C-1 the odontoid, and the dura, both anterior and posterior to the spinal cord. Hall and Selin[4] reported a patient in whom the urate deposits were in the facets and synovial membranes of the fourth and fifth lumbar vertebrae. The patient did not complain of low back or radicular pain. Lichtenstein and co-workers[3] performed extensive autosy examinations of 11 patients with gout. They found urate deposits in lumbar disks and adjacent vertebral bodies in only one patient.

This investigation was supported by Public Health Service grant NS-04053 from the National Institute of Neurological and Communicative Disorders.

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News and Comment

CALENDAR OF MEETINGS

1976		
Dec	3-4	Association for Research in Nervous and Mental Disease, annual meeting, Hotel Roosevelt, New York
1977		
Jan	23-29	Southern Clinical Neurological Society, fourth meeting, Pier 66, Ft Lauderdale, Fla
Feb	25-26	Second Annual Joint Stroke Conference, Sheraton 4-Ambassadors Hotel, Miami
April	24-28	American Association of Neurological Surgeons, annual meeting, Four Seasons Hotel, Toronto
June	19-25	World Federation of Neurosurgical Societies, Sixth International Congress of Neurological Surgery, Sao Paulo, Brazil
July	18-23	27th International Congress of Physiological Sciences, Paris

Annual Research in Nervous and Mental Disease Meeting.—The Association for Reaserch in Nervous and Mental Disease, Inc, will hold its annual meeting at the Hotel Roosevelt in New York City on Dec 3 and 4, 1976. This year's meeting will be devoted to the hypothalamus. Topics to be discussed include the morphology of the endocrine hypothalamus, the peptides of the hypothalamus, peptide and steroid receptors in brain, the functional significance of the extra-hypothalamic distribution of the releasing hormones, neuroendocrine function and disorder in human will, visceral and behavioral aspects of human hypothalamic disease, and the hypothalamic pituitary control systems for growth hormone and gonadotrophic hormone.

Information can be obtained from Dr Roger C Duvoisin, Association for Research in Nervous and Mental Disease, Inc, 100th Street at Fifth Avenue, New York, NY 10029.

Postdoctoral Fellowships.—The Clinical Neuroscience Research Center of the Departments of Neurology and Neurosurgery at the University of Virginia School of Medicine offers National Institutes of Health fellowships for postdoctoral training in developmental neurology to qualified applicants holding an MD, PhD, or equivalent degree. The program is designed to provide interdisciplinary training opportunities in neuroanatomy, electron microscopy, histochemistry, neurophysiology, neural modeling, neurochemistry, and neuropharmacology as part of basic research and neuromuscular disease. Immediate openings exist for three candidates at stipends ranging from $10,000 to $14,000. Send applications and curriculum vitae to Dr Norman H. Bass, Department of Neurology, University of Virginia School of Medicine, Charlottesville, VA 22901.

Pathogenesis and Treatment of Headache.—A course entitled "Continuing Education in Pathogenesis and Treatment of Headache in Adults and Children" will be given on Jan 7 through 9, 1977. It is AMA category 1 accredited and sponsored by the American Association for the Study of Headache and the National Migraine Foundation; the Department of Neurology, University of New Mexico School of Medicine; and the Scripps Clinic and Research Foundation. For information write Otto Appenzeller, MD, PhD, Course Director, Department of Neurology, University of New Mexico, School of Medicine, Albuquerque, NM 87131.

Fourth Southern Clinical Neurological Society Meeting.—The next meeting of the Southern Clinical Neurological Society is Jan 23 through 29, 1977, at Pier 66, PO Drawer 9177, Ft Lauderdale, FL 33310. The Society is now accepting abstracts of papers for this meeting. Inquiries about membership, abstracts, and information about the coming meeting may be obtained from Dr Beauregard Bercaw, 1011 Jeffords, Clearwater, FL 33516.

Second Annual Course in Behavioral Neurology and Neuropsychology.—The Florida Society of Neurology is sponsoring the Second Annual Course in Behavioral Neurology and Neuropsychology to be held in Orlando, Fla, on Dec 2 through 4, 1976. Subjects to be covered include aphasia, apraxia, visual-spatial disorders, amusia, emotional disturbances from right hemispheric lesions, agnosia, neglect syndrome, and memory. Cochairmen are Drs Kenneth M. Heilman and Edward Valenstein, Department of Neurology, University of Florida, J. Hillis Miller Health Center, Gainesville, FL 32610.

Journal of Computer Assisted Tomography.—Dr Giovanni De Chiro will edit a new quarterly periodical, *Journal of Computer Assisted Tomography*. Publication by Raven Press will begin in January 1977. Dr De Chiro is on the staff of the National Institutes of Health, Bldg 10, Room 2D13, Bethesda, MD 20014.

Current Therapy of Common Neurological Disorders.—This postgraduate seminar will be held Dec 10 and 11, 1976, at the University of Texas Health Science Center at Dallas, Southwestern Medical School. It is presented by the Department of Neurology (Roger N. Rosenberg, MD, chairman) and designed for the neurologist, internist, pediatrician, and family practice physician. The course is approved for 12 hours of credit in category 1 toward the Physician's Recognition Award of the AMA. For further information, please write to Office of Continuing Education, The University of Texas Health Science Center, 5323 Harry Hines Blvd, Dallas, TX 75235.

Symposium on the Reliable Quantification of Antiepileptic Drugs.—A Symposium on the Reliable Quantification of Antiepileptic Drugs will be held Nov 29 through Dec 1, 1976, in Kansas City, Mo. It is sponsored by the National Institute of Neurological and Communicative Disorders and Stroke (C. E. Pippinger, chairman) and by the Epilepsy Foundation of America (David Daly, chairman) in cooperation with the Joint Committee on the Measurement of In Vivo Drug Levels. Methods of assay, laboratory variability, and clinical application will be reviewed. For further information contact Lawrence D. Smith, Secretary, Federal Building, Room 114, NINCDS, Bethesda, MD 20014.

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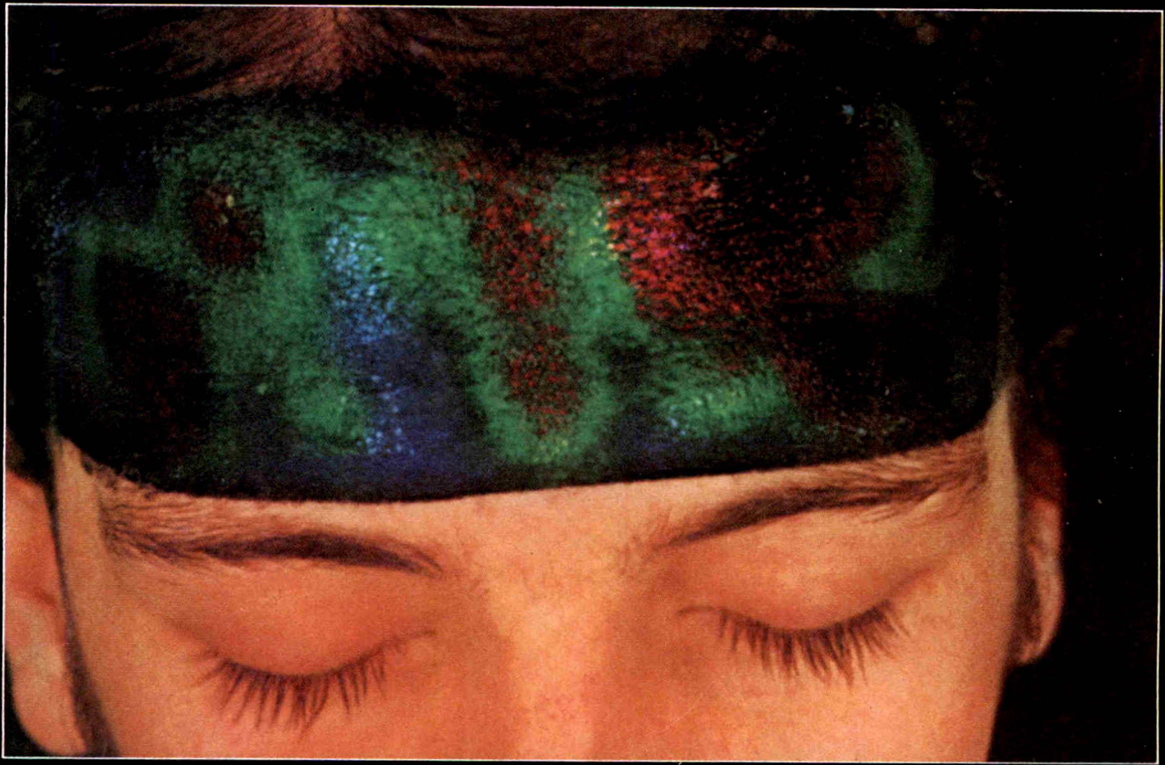
The mapping of a migraine



Specific vascular changes are revealed by liquid crystalography

Liquid crystal thermography dynamically demonstrates the unilateral surface temperature changes reflective of the dilation of deep cerebral arteries during a migraine attack. Liquid crystals allow differences in skin temperature to be "mapped" directly on the subject. Variations in skin heat loss are registered immediately, enabling rapid temperature changes to be followed easily. (Red reflects the coolest temperature, then green, blue, and violet.)

This picture was taken of a migraine sufferer during an attack. The colors over the left eye reflect the cooler skin temperature due to the unilateral decreased blood flow to the forehead skin vessels that results from dilation of cerebral vessels on the affected side.

Specific therapy for migraine complicated by tension and G.I. upset

The combined vasoconstrictive actions of ergotamine and caffeine offer the best therapeutic results in helping to abort or relieve the migraine headache. Additionally, belladonna alkaloids help relieve the accompanying gastrointestinal irritability. And the patient's nervous tension, perhaps a precipitating factor in the onset of an attack, is often allayed by the pentobarbital in Cafergot P-B.

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TABLETS: Gynergen® (ergotamine tartrate, U.S.P.) 1 mg.; caffeine, U.S.P., 100 mg.; Bellafoline® (levorotatory alkaloids of belladonna, as malates) 0.125 mg.; sodium pentobarbital, U.S.P., (*Warning:* May be habit forming) 30 mg.
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Contraindications: Peripheral vascular disease, coronary heart disease, hypertension, impaired hepatic or renal function, sepsis, and pregnancy. Hypersensitivity to any of the components.

Precautions: Although signs and symptoms of ergotism rarely develop even after long term intermittent use of the orally or rectally administered drugs, care should be exercised to remain within the limits of recommended dosage.

Adverse Reactions: Numbness and tingling of fingers and toes, muscle pains in the extremities, weakness in the legs, precordial distress and pain, transient tachycardia or bradycardia, nausea, vomiting, localized edema, and itching. Drowsiness may occur with Cafergot P-B.

Adult Dosage: *Orally*—Two tablets at first sign of attack; if needed, 1 additional tablet every half hour until relieved (maximum, 6 per attack or 10 per week). *Rectally*—One suppository as early as possible in attack; second in 1 hour, if needed (maximum, 2 per attack or 5 per week).

Overdosage: Symptoms include vomiting; numbness, tingling, pain and cyanosis of the extremities associated with diminished or absent peripheral pulses; hypertension or hypotension; drowsiness, stupor, coma, convulsions and shock. A case has been reported of reversible bilateral papillitis with ring scotomata in a patient who received five times the recommended daily adult dose over a period of 14 days. Treatment consists of induction of emesis, gastric lavage, and catharsis; maintenance of adequate pulmonary ventilation; correction of hypotension; and control of convulsions. Treatment of peripheral vasospasm should consist of warmth, but not heat, and protection of the ischemic limbs. Vasodilators may be used with benefit but caution must be exercised to avoid aggravating an already existent hypotension.

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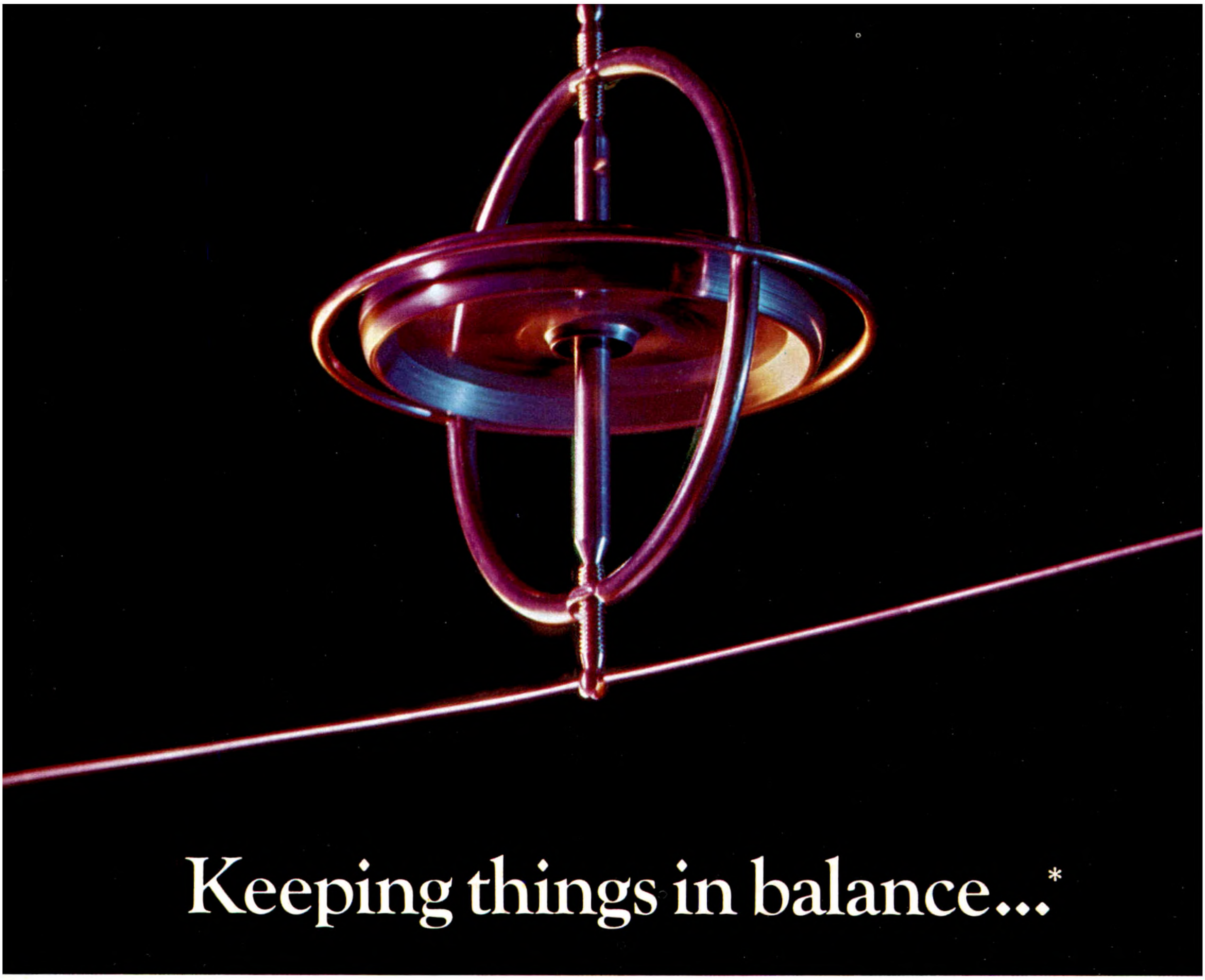

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Usage in Pregnancy: See "Contraindications."

ADVERSE REACTIONS. Drowsiness, dry mouth and, on rare occasions, blurred vision have been reported.

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The vulnerable ages

The first epileptic seizure is most likely to occur during early childhood and at the onset of puberty

About 9 out of 10 epileptics experience their first seizure before the age of 20—with the highest incidence between 5 and 7, when children start school, and at the onset of puberty, a time of physiological and psychic turmoil.[1] The most common type, grand mal, occurs in approximately 75% of epileptic children,[1] and more than 50% of patients who suffer initially from petit mal develop grand mal seizures before they reach the age of 16.[2]

Mysoline (primidone) for control of grand mal, psychomotor and focal epilepsy

At the onset and afterwards— used alone or as concomitant therapy, MYSOLINE may reduce the frequency and severity of major motor seizures—or even eliminate them. *Excellent* for control of grand mal. Valuable for control of psychomotor[1,3,4] and focal epilepsy as well.[5]

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Change to Mysoline when other anticonvulsants fail— A changeover to MYSOLINE is frequently warranted when other anticonvulsants must be discontinued because of important side effects, or when grand mal seizures are refractory to phenobarbital, with or without diphenylhydantoin.[7]

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50 mg.
Suspension 250 mg./5 cc.

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initial and maintenance therapy for
grand mal, psychomotor and focal epilepsy

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ACTIONS: MYSOLINE acts on the central nervous system to raise seizure threshold or alter seizure pattern. The mechanism(s) of action of anticonvulsant drugs is not known.

Primidone has anticonvulsant activity *per se.* In addition, its two metabolites possess anticonvulsant qualities. The major metabolite is phenylethylmalonamide (PEMA); the other is phenobarbital. In addition to its own anticonvulsant potential, PEMA potentiates phenobarbital.

INDICATIONS: MYSOLINE, either alone or used concomitantly with other anticonvulsants, is indicated in the control of grand mal, psychomotor, and focal epileptic seizures. It may control grand mal seizures refractory to other anticonvulsant therapy.

CONTRAINDICATIONS: Primidone is contraindicated in: 1) patients with porphyria and 2) patients who are hypersensitive to phenobarbital (see ACTIONS).

WARNINGS: The abrupt withdrawal of antiepileptic medication may precipitate status epilepticus.

The therapeutic efficacy of a dosage regimen takes several days before it can be assessed.

Use in pregnancy: Recent reports strongly suggest an association between the use of anticonvulsant drugs by women with epilepsy and an elevated incidence of birth defects in children born to these women. Reference has been made to primidone in several cases in which it was used *in combination* with other anticonvulsants; but its teratogenicity has not been conclusively demonstrated. The possibility exists that other factors, *e.g.*, genetic factors or the epileptic condition, may contribute to the higher incidence of birth defects. The data also indicate that the great majority of mothers receiving anticonvulsant medication deliver normal infants.

Anticonvulsant drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and risk to both mother and the unborn child.

When the nature, frequency, and severity of the seizures do not pose a clear threat to the patient, good medical practice requires that the physician weigh the expected therapeutic benefit of anticonvulsant therapy against possible risk on an individual basis.

Neonatal hemorrhage, with a coagulation defect resembling vitamin K deficiency, has been described in newborns whose mothers were taking primidone and other anticonvulsants. Pregnant women under anticonvulsant therapy should receive prophylactic vitamin K_1 therapy for one month prior to, and during, delivery.

The physician should weigh all of the foregoing considerations when treating and counseling epileptic women of childbearing potential.

PRECAUTIONS: The total daily dosage should not exceed 2 Gm. Since MYSOLINE therapy generally extends over prolonged periods, a complete blood count and a sequential multiple analysis-12 (SMA-12) test should be made every six months.

In nursing mothers: There is evidence that in mothers treated with primidone, the drug appears in the milk in substantial quantities. Since tests for the presence of primidone in biological fluids are too complex to be carried out in the average clinical laboratory, it is suggested that the presence of undue somnolence and drowsiness in nursing newborns of MYSOLINE-treated mothers be taken as an indication that nursing should be discontinued.

ADVERSE REACTIONS: The most frequently occurring early side effects are ataxia and vertigo. These tend to disappear with continued therapy, or with reduction of initial dosage. Occasionally, the following have been reported: nausea, anorexia, vomiting, fatigue, hyperirritability, emotional disturbances, sexual impotency, diplopia, nystagmus, drowsiness, and morbilliform skin eruptions. Occasionally, persistent or severe side effects may necessitate withdrawal of the drug. Megaloblastic anemia may occur as a rare idiosyncrasy to MYSOLINE and to other anticonvulsants. The anemia responds to folic acid, 15 mg. daily, without necessity of discontinuing medication.

DOSAGE AND ADMINISTRATION: The average adult dose is 0.75 to 1.5 Gm. per day. The initial dose is 250 mg. Increments of 250 mg. are added, usually at weekly intervals, to tolerance, or therapeutic effectiveness, up to daily doses not exceeding 2.0 Gm. A typical dosage schedule for the introduction of MYSOLINE (primidone) is as follows:

Adults and Children Over 8 Years of Age

1st Week 250 mg. daily at bedtime	*2nd Week* 250 mg. b.i.d.
3rd Week 250 mg. t.i.d.	*4th Week* 250 mg. q.i.d.

In children under 8 years of age, maintenance levels are established by a similar schedule, but at one-half the adult dosage. It is best to begin with 125 mg., with gradual weekly increases of 125 mg. a day, to a daily total usually between 500 mg. and 750 mg.

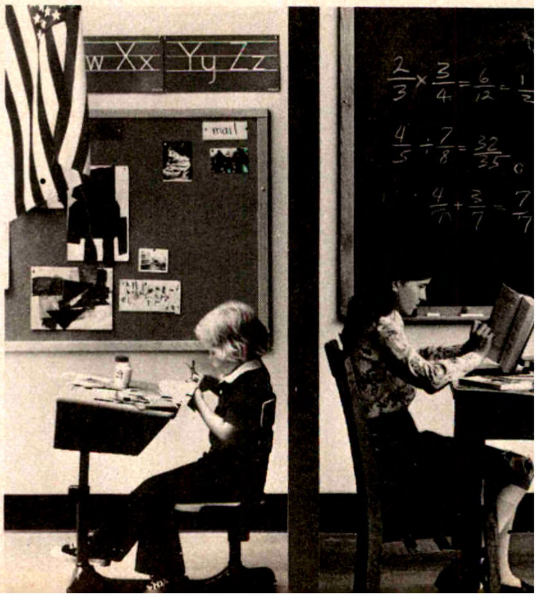
In patients already receiving other anticonvulsants: MYSOLINE should be gradually increased as dosage of the other drug(s) is maintained or gradually decreased. This regimen should be continued until satisfactory dosage level is achieved for combination, or the other medication is completely withdrawn. When therapy with this product alone is the objective, the transition should not be completed in less than two weeks.

MYSOLINE 50 mg. Tablet can be used to practical advantage when small fractional adjustments (upward or downward) may be required, as in the following circumstances:

- for initiation of combination therapy
- during "transfer" therapy
- for added protection in periods of stress or stressful situations that are likely to precipitate seizures (menstruation, allergic episodes, holidays, etc.)

HOW SUPPLIED: MYSOLINE *Tablets*—No. 430—Each tablet contains 250 mg. of primidone (scored), in bottles of 100 and 1,000. Also in unit dose package of 100. No. 431—Each tablet contains 50 mg. of primidone (scored), in bottles of 100 and 500. MYSOLINE *Suspension*—No. 3850—Each 5 cc. (teaspoonful) contains 250 mg. of primidone, in bottles of 8 fluidounces.

References: 1. Livingston, S.: Comprehensive Management of Epilepsy in Infancy, Childhood and Adolescence, Springfield, Ill., Charles C Thomas, 1972, pp. 6, 7, 584. 2. Grossman, H.J.: Ill. Med. J. *135*:260 (Mar.) 1969. 3. Scholl, M.L., in Conn, H.F.: Current Therapy 1973, Philadelphia, Saunders, 1973, pp. 675-7. 4. Metrick, S.: C.M.D. *37*:49 (Jan.) 1970. 5. Forster, F.M.: Med. Clin. North Am. *47*:1579 (Nov.) 1970. 6. White, P.T.: Wis. Med. J. *68*:178 (Apr.) 1969. 7. Millichap, J.G.: Drug Ther. *1*:15 (Oct.) 1971.



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Imbalance

a central problem
in the management of Parkinson's disease

Posed by professional models.

by helping to correct
dopamine/acetylcholine imbalance

Sinemet®

a combination of carbidopa and levodopa

may help bring the world of the
parkinsonian patient back into balance

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See last page of advertisement for brief summary of prescribing information.

Sinemet®

a combination of
carbidopa and levodopa

can mean a world of difference for some parkinsonian patients...

Symptomatic relief

SINEMET usually relieves the major symptoms of Parkinson's disease:

- **rigidity**
- **bradykinesia**
- **tremor**

Improved performance of daily activities

Symptomatic relief of Parkinson's disease may enable some patients to carry out such routine daily activities as:

- **dressing**
- **walking**
- **eating**
- **maintaining personal hygiene**

SINEMET is contraindicated in:

Patients receiving monoamine oxidase inhibitors. These inhibitors must be discontinued at least two weeks prior to initiating therapy with SINEMET.

Patients with known hypersensitivity to this drug.

Patients with narrow-angle glaucoma. (Patients with chronic wide-angle glaucoma may be treated cautiously if intraocular pressure is well controlled and the patient is monitored carefully for changes in intraocular pressure during therapy.)

Patients with suspicious, undiagnosed skin lesions or a history of melanoma. Because levodopa may activate a malignant melanoma, SINEMET should not be used in these patients.

All cautionary information with levodopa also applies to SINEMET. Turn to the last page for additional information.

and that difference often depends on proper dosage

Start with SINEMET-25/250 containing 25 mg carbidopa and 250 mg levodopa for patients transferred from levodopa

SINEMET-25/250 t.i.d. or q.i.d. is the suggested starting dosage for most patients. And, since most patients can be maintained on only one or two tablets t.i.d., SINEMET-25/250 is the most convenient strength.

Enough carbidopa

A daily dosage of SINEMET should be chosen that will provide approximately 70 to 100 mg of carbidopa because studies show that peripheral dopa decarboxylase is saturated by carbidopa at approximately 70 to 100 mg per day.

SINEMET-25/250 is the most convenient strength for providing the proper amount of carbidopa necessary for optimal therapeutic response. For example, one SINEMET-25/250 t.i.d. provides 75 mg of carbidopa—an adequate amount of carbidopa for maximum utilization of levodopa, with less nausea and vomiting.

Enough levodopa

A daily dosage of SINEMET should be chosen that will provide approximately 25 percent of the previous levodopa daily dosage.

SINEMET-25/250 is the most convenient strength for providing the proper amount of levodopa. For example, one SINEMET-25/250 t.i.d. provides 750 mg of levodopa—the proper amount of levodopa for patients previously on 3000 mg of levodopa.

SINEMET-10/100, containing 10 mg carbidopa and 100 mg levodopa, is the preferred strength for patients who are not on levodopa or for patients on levodopa who have been taking less than 1500 mg per day.

Start with SINEMET-10/100 t.i.d and increase by 1 tablet every day or every other day until a dosage of 6 tablets is reached. If further titration is necessary, *change* the patient to SINEMET-25/250, at a dosage of 1 tablet t.i.d.

NOTE: Most patients on SINEMET will eventually require SINEMET-25/250 for optimal control of the symptoms of Parkinson's disease.

Other dosage considerations

Discontinue levodopa at least 8 hours before SINEMET is begun. A time interval shorter than 8 hours may increase the risk of levodopa-induced adverse reactions.

Because of increased brain dopamine levels, both therapeutic and adverse reactions (specifically, involuntary movements and mental disturbances) occur at lower doses and more rapidly with SINEMET than with levodopa. In order to reduce adverse reactions, it is necessary to individualize therapy and to monitor the patient closely during the dose adjustment period. The occurrence of involuntary movements may require dosage reduction. Blepharospasm may be a useful sign of excess dosage in some patients.

Instruct patients not to take levodopa with SINEMET unless you specifically recommend it.

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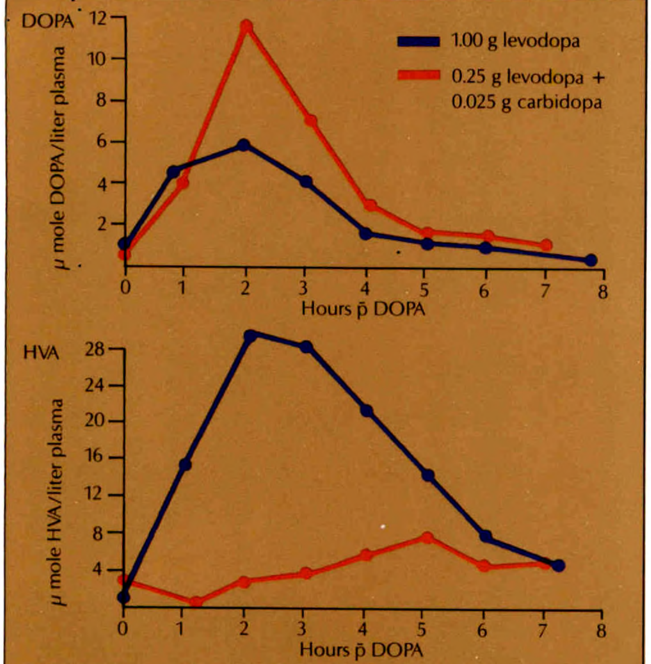
See following page for brief summary of prescribing information.

Carbidopa: a key ingredient in SINEMET



Levodopa alone vs. levodopa plus a decarboxylase inhibitor–carbidopa.

By measuring the blood levels of dopa and its primary metabolite, homovanillic acid, the difference between giving a dose of levodopa alone and combining a dose with carbidopa can be shown. When levodopa is given alone, there is a gradual rise and fall of the levodopa blood level. Since it is being metabolized peripherally, homovanillic acid begins to rise soon after levodopa enters the blood and continues to do so over a three- or four-hour period. When one-fourth the amount of levodopa is given with 25 mg of carbidopa, not only is there a higher blood level from less levodopa, but its conversion to homovanillic acid is inhibited.

When SINEMET is to be given to patients who are being treated with levodopa, levodopa must be discontinued at least 8 hours before therapy with SINEMET is started. In order to reduce adverse reactions, it is necessary to individualize therapy. See the Warnings (below) and Dosage and Administration sections in the full prescribing information before initiating therapy.

Contraindications: MAO inhibitors and SINEMET should not be given concomitantly. MAO inhibitors must be discontinued at least 2 weeks prior to initiating therapy with SINEMET.

SINEMET is contraindicated in patients with known hypersensitivity to this drug and in narrow-angle glaucoma.

Because levodopa may activate a malignant melanoma, it should not be used in patients with suspicious, undiagnosed skin lesions or history of melanoma.

Warnings: Levodopa must be discontinued at least 8 hours before SINEMET is started. SINEMET should be substituted at a dosage that will provide approximately 25 percent of the previous levodopa dosage. (See Dosage and Administration section of full prescribing information.) Patients taking SINEMET should be instructed not to take additional levodopa unless prescribed.

As with levodopa, SINEMET may cause involuntary movements and mental disturbances. These reactions may be due to increased brain dopamine following administration of levodopa. All patients should be observed carefully for development of depression with concomitant suicidal tendencies. Treat with caution patients with past or current psychoses. *Because carbidopa permits more levodopa to reach the brain and, thus, more dopamine to be formed, dyskinesias may occur at lower dosages and sooner with SINEMET than with levodopa.* Occurrence of dyskinesias may require dosage reduction.

SINEMET should be administered cautiously to patients with severe cardiovascular or pulmonary disease, bronchial asthma, renal, hepatic or endocrine disease.

Exercise care in administering SINEMET, as with levodopa, to patients with history of myocardial infarction who have residual atrial, nodal, or ventricular arrhythmias. In such patients, cardiac function should be monitored with particular care during period of initial dosage adjustment, in a facility with provisions for intensive cardiac care.

As with levodopa, there is possibility of upper G.I. hemorrhage in patients with history of peptic ulcer.

Usage in Pregnancy and Lactation: Although effects of SINEMET on human pregnancy and lactation are unknown, both levodopa and combinations of carbidopa and levodopa have caused visceral and skeletal malformations in rabbits. Use of SINEMET in women of childbearing potential requires that anticipated benefits of the drug be weighed against possible hazards to mother and child. SINEMET should not be given to nursing mothers.

Usage in Children: Safety of SINEMET in patients under 18 has not been established.

Precautions: As with levodopa, periodic evaluations of hepatic, hematopoietic, cardiovascular, and renal function are recommended during extended therapy.

Patients with chronic wide-angle glaucoma may be treated cautiously with SINEMET provided intraocular pressure is well controlled and patient is monitored carefully for changes in intraocular pressure during therapy.

Symptomatic postural hypotension can occur. For this reason, SINEMET should be given cautiously to patients on antihypertensive drugs. When SINEMET is started, dosage adjustment of the antihypertensive drug may be required. (For patients receiving pargyline, see the contraindication on MAO inhibitors.)

Since phenothiazines and butyrophenones may reduce therapeutic effects of levodopa, they should be administered with caution if concomitant administration with SINEMET is necessary, and patients should be carefully observed for loss of antiparkinsonian effect.

Adverse Reactions: Most common serious adverse reactions occurring with SINEMET are choreiform, dystonic, and other involuntary movements. Other serious adverse reactions are mental changes including paranoid ideation and psychotic episodes, depression with or without development of suicidal tendencies, and dementia. Convulsions also have occurred; however, a causal relationship with SINEMET has not been established.

A common but less serious effect is nausea.

Less frequent adverse reactions are cardiac irregularities and/or palpitations, orthostatic hypotensive episodes, bradykinetic episodes (the "on-off" phenomenon), anorexia, vomiting, and dizziness.

Rarely, G.I. bleeding, development of duodenal ulcer, hypertension, phlebitis, hemolytic anemia, leukopenia, and agranulocytosis have occurred.

Other adverse reactions reported with levodopa include dry mouth, dysphagia, sialorrhea, abdominal pain and distress, ataxia, increased hand tremor, headache, numbness, weakness and faintness, bruxism, confusion, insomnia and nightmares, hallucinations and delusions, agitation and anxiety, malaise, fatigue, euphoria, muscle twitching and blepharospasm (may be taken as an early sign of excess dosage; consider dosage reduction at this time), trismus, burning sensation of tongue, bitter taste, diarrhea, constipation, flatulence, flushing, skin rash, increased sweating, bizarre breathing patterns, urinary retention, urinary incontinence, diplopia, blurred vision, dilated pupils, hot flashes, weight gain or loss, dark sweat and/or urine, oculogyric crises, sense of stimulation, hiccups, edema, loss of hair, hoarseness, priapism, and activation of latent Horner's syndrome.

Abnormalities in laboratory tests may include elevations of blood urea nitrogen, SGOT, SGPT, lactic dehydrogenase, bilirubin, alkaline phosphatase, protein-bound iodine, and positive Coombs test. More commonly, levels of blood urea nitrogen, creatinine, and uric acid are lower during administration of SINEMET than with levodopa.

Overdosage: Management of acute overdosage with SINEMET is basically the same as management of acute overdosage with levodopa; however, pyridoxine is not effective in reversing the actions of SINEMET.

How Supplied: Tablets SINEMET-10/100 and Tablets SINEMET-25/250 are supplied in bottles of 100.

For more detailed information, consult your MSD representative or see full prescribing information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486.

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Hartnup Disease

Clinical, Pathological, and Biochemical Observations

Albert J. Tahmoush, MD; David H. Alpers, MD; Ralph D. Feigin, MD;
Vernon Armbrustmacher, MD; Arthur L. Prensky, MD

• Hartnup disease is a rare genetic disorder of amino acid transport associated with variable and intermittent clinical abnormalities. A family is described in which three siblings had an intermittently progressive neurological disease and two of the affected siblings had the Hartnup-pattern aminoaciduria. Neuropathological examination of one case showed severe diffuse atrophy, generalized neuronal loss in the cortex, and Purkinje cell loss in the cerebellum. In vivo and in vitro studies of intestinal amino acid transport in the surviving sibling indicated a partial defect in the transport of several neutral amino acids (tryptophan, alanine, serine, and methionine) with normal transport of other neutral amino acids (threonine, phenylalanine, histidine, tyrosine, and isoleucine). Transport of glycine, proline, hydroxyproline, and the basic amino acids appeared normal.

(*Arch Neurol* 33:797-807, 1976)

Hartnup disease is a rare genetic disorder characterized by a defect in both the renal tubular reabsorption and intestinal transport of amino acids.[1-3] The renal tubular defect results in an aminoaciduria with increased amounts of the neutral amino acids (alanine, serine, glutamine, valine, leucine, isoleucine, phenylalanine, tyrosine, tryptophan, and histidine), moderately increased amounts of glycine and basic amino acids (cystine and lysine), and no detectable excretion of proline and hydroxyproline. This pattern of increased urinary amino acids (Hartnup-pattern aminoaciduria) is the most specific abnormality by which Hartnup disease can be identified.[4] A similar pattern of increased amounts of amino acids in the feces results from the intestinal transport defect.[5]

The clinical abnormalities present in Hartnup disease are variable and generally intermittent. Episodes of a pellagra-like skin rash and cerebellar ataxia in combination with progressive dementia and spasticity were the most prominent signs in the propositus first described by Baron et al.[4] A sister of the propositus had similar intermittent episodes but no residual neurological abnormalities, and two younger siblings were described as normal. Forty-four additional patients in 24 families have been reported with the Hartnup-pattern aminoaciduria.[6-28] Twenty-five of these patients had attacks in which a variable combination of neuropsychiatric and dermatological abnormalities occurred similar to those described in the propositus.[6-24] Mental retardation was the only clinical abnormality in four patients,[25,26] and 15 patients had no clinical abnormalities.[10,13,15,17,26-28]

To our knowledge, the pathological findings in patients with symptomatic Hartnup disease have not been reported. Autopsy examination of a patient reported to have Hartnup disease is present in the literature.[29] However, a generalized and not the Hartnup-pattern aminoaciduria was described, and the clinical picture was unusual with bouts of fever and abdominal pain.

The characteristics of the intestinal amino acid transport defect present in Hartnup disease have not been completely defined. Review of the literature shows that only 10 of the 48 patients have had intestinal transport studies and that these studies have been limited to only a small number of amino acids. Oral tryptophan loading consistently results in lower plasma

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Reprint requests to Walter Reed Army Institute of Research, Washington, DC 20012 (Dr Tahmoush).

tryptophan levels in Hartnup patients than controls,[10,14,25,30] but the intestinal transport of other amino acids is not consistently abnormal.[14,25-27,31,32]

In this report, a family is described in which three of eight siblings had an intermittently progressive neurological disease. The Hartnup-pattern aminoaciduria was present in the two examined siblings. One patient died of pneumonia, and a complete pathological examination was performed, which included ultrastructural and tissue culture studies. The intestinal transport of amino acids was studied in the surviving sibling.

REPORT OF CASES

Case 1.—An 18-year-old woman (Fig 1, right) was referred in March 1970 with a history of mental retardation and progressive neurological abnormalities. She was the product of a full-term pregnancy and normal delivery. Early motor development was slow. At age 7, she had an intelligence quotient of 63 as determined by the Binet test. The patient learned to read simple words and showed progressive improvement in motor coordination during the next three years. From 11 to 18 years of age, no significant change in psychomotor performance was apparent. In the three months preceding admission, psychomotor function deteriorated rapidly with complete loss of purposeful movements and partial loss of speech.

Physical examination revealed an agitated patient who spontaneously repeated the phrases, "I'm scared," "Matt Powers," and "Ben Casey." Weight was 42.4 kg, and height 161 cm. Findings from general examination were normal. On neurological examination, the patient was awake but did not respond appropriately to questions or simple commands. The cranial nerves were intact, and findings from funduscopic examination were normal. Muscle bulk and tone were normal. Symmetrical hyperreflexia and flexor plantar responses were present. Spontaneous movements were slow and infrequent. Painful stimuli elicited an appropriate withdrawal reaction, but other sensory modalities could not be tested.

On admission, findings from the following were all within normal limits: complete blood cell count (CBC), urinalysis, VDRL, blood chemistry studies, serum protein electrophoretic pattern, serum immunoglobulin concentrations, arterial pH, T_4 level, blood ammonia, blood lead, serum B_{12}, and serum ceruloplasmin. The ECG, chest roentgenograms, and intravenous urogram also showed no abnormalities. The creatinine clearance, insulin clearance, and tubular reabsorption of phosphate were within the normal range.

Paper chromatography of blood and CSF indicated a normal amino acid pattern on two occasions. Paper chromatography of urine on two occasions showed the Hartnup-pattern aminoaciduria. Screening tests for urinary reducing substances and mucopolysaccharides were negative. Chromatography for urinary indoles indicated heavy spots for urea, tryptophan, and indolyl sulfate and trace spots for indolyl acetic acid and 5-hydroxy indolyl acetic acid. Paper chromatography performed on the ultrafiltrate of a 24-hour stool collection showed increased amounts of alanine, serine, threonine, valine, leucine-isoleucine, glutamine, histidine, glycine, lysine, and glutamic acid.

Electroencephalograms performed on two occasions were mildly disordered with diffuse slow activity. A lumbar puncture showed colorless fluid with no cells and normal glucose level, protein level, and protein electrophoretic pattern. An electromyelogram showed no abnormal muscle activity. The peroneal and ulnar nerve conduction times, skull roentgenograms, and brain scan were normal. Minimal cortical and moderate cerebellar atrophy were noted on pneumoencephalography.

There was no evidence of a generalized malabsorption syndrome. Results from a serum carotene and vitamin A determinations, five-hour oral glucose tolerance test, three-hour lactose tolerance test, and D-xylose tolerance test were normal. An upper gastrointestinal series and small bowel study showed no abnormalities. Histological examination of jejunal biopsy tissue revealed normal villi and submucosa.

The patient's clinical status deteriorated rapidly during hospitalization. Complete loss of speech occurred, and vocalization was limited to high-pitched cries. Dystonic postures of the trunk and athetoid movements of the extremities developed. Hyperreflexia became more prominent, and unsustained clonus at the ankles was noted. Rigid hypertonia, symmetrical muscle atrophy, and flexion contractures were present three months later. Pharmacologic doses of niacinamide were administered for one year without clinical improvement, and briefer trials of ascorbic acid and pyridoxine hydrochloride were also without benefit.

Between July 1970 and December 1972, no change in clinical status was noted. Aminoaciduria was not present in July 1971, and all subsequent urine examinations have contained a normal concentration of amino acids. In July 1972, histochemical studies of a right quadriceps muscle biopsy specimen showed considerable type II atrophy. Marked increase in cortical atrophy and diffuse ventricular enlargement were seen on repeat pneumoencephalography.

Case 2.—A 21-year-old man (Fig 2, right) was admitted on March 16, 1970. He was the product of a full-term pregnancy and normal delivery. The older siblings remembered the patient as always being slow and of short stature. At 6 years of age, neurological examination indicated mental retardation and motor incoordination. An EEG contained three-per-second atypical spike and wave activity. The patient remained stable up to age 11 when a rapid deterioration of psychomotor development began characterized by emotional lability, loss of speech, and inability to walk. By age 12, he was bedfast, incontinent, and required tube feedings. During the next nine years, the patient's condition remained unchanged.

On admission, physical examination revealed a thin man with the appearance and size of an 8-year-old boy (Fig 2, right). The patient had a tracheostomy scar, marked kyphoscoliosis, no facial or axillary hair, minimal pubic hair, and prepubertal testes. He was awake, but responsive only to painful stimulation. Guttural sounds, dystonic posture of the trunk, and athetoid movements of the extremities occurred spontaneously. The pupils reacted to light, but visual fixation and following movements to large objects were not obtained. Doll's head maneuver elicited full extraocular movements. There was bilateral optic atrophy. The remainder of the cranial nerves were normal. Examination of the extremities showed symmetric muscle atrophy, severe joint contractures, rigid hypertonia, hyperreflexia, spontaneous clonus, and flexor plantar responses.

Findings from CBC, urinalysis, VDRL, blood chemistry studies, ECG, T_4 determination, glucose tolerance test, serum protein electrophoretic pattern, serum ceruloplasmin determination, 24-hour urine 17-hydroxy and 17-ketosteroid determinations, metapyrone stimulation and arginine infusion tests were within normal limits. Skull roentgenograms showed generalized demineralization, and bone age was 12½ years as calculated by the method of Greulich and Pyle.

Paper chromatography of blood showed a normal amino acid pattern on two occasions. Paper chromatography of urine on two occasions showed the Hartnup-pattern aminoaciduria. Paper chromatograms for urine indoles resulted in heavy spots for urea, tryptophan, and indoxyl sulfate plus

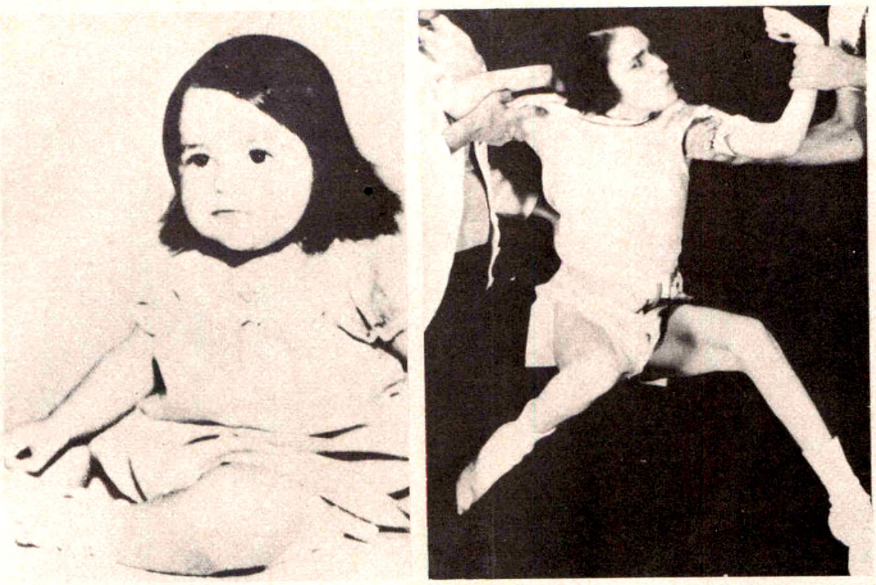
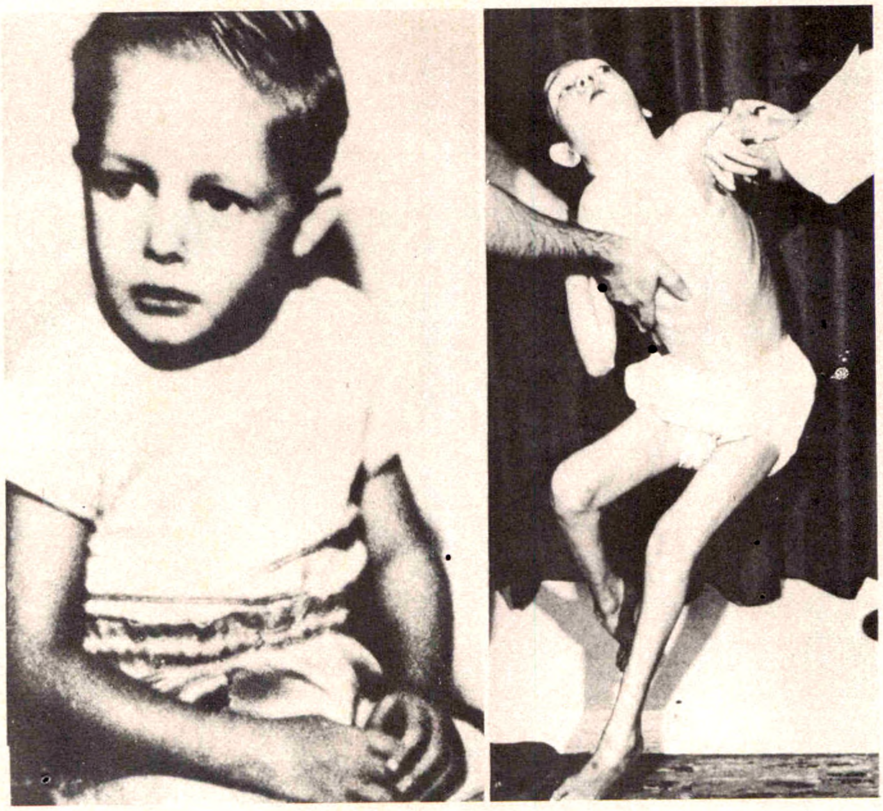


Fig 1.—Patient 1 before and after progressive neurological deterioration. Left, At age 18 months. Right, At age 18 years.

Fig 2.—Patient 2 before and after progressive neurological deterioration. Left, At age 5 years. Right, At age 21 years.



trace spots for indolyl acetic acid and 5-hydroxy indolyl acetic acid.

Electroencephalograms on two occasions contained diffuse slow activity. A lumbar puncture showed colorless fluid with no cells and a normal glucose level, protein level, and protein electrophoretic pattern. A pneumoencephalogram demonstrated mild ventricular enlargement plus marked cortical and cerebellar atrophy.

A left frontotemporal craniotomy was performed with biopsy of the anterior tip of the temporal lobe and inferior frontal lobe. Histological examination and ultrastructural studies of the cortical biopsy specimen showed normal cell bodies, axons, and nerve endings. Tissue culture of biopsy material, employing the Maximow double coverslip assembly, revealed no morphological abnormalities of glial cells.

The patient developed pneumonia and died on the 23rd hospital day. Postmortem examination was performed.

Case 3.—The clinical records of a deceased elder sibling with a similar neurological disease were reviewed. Early development was slow. At 9 years of age, she had a short attention span and poor motor coordination. Her mental age was 3½ years as determined by the Stanford-Binet test. During the next six years, her behavior became unpredictable with episodes of agitation and destructiveness. Loss of purposeful movements, loss of interest in her surroundings, disappearance of speech, and progressive rigidity with severe flexion contractures of all extremities occurred between 15 and 19 years of age. She was reduced to a vegetative state by age 21 and died at age 34 of pneumonia. There was no postmortem examination.

PEDIGREE OF THE KINDRED

A family history of 34 members in four generations (Fig 3) showed no significant neuropsychiatric illness with the exception of a 60-year-old paternal second cousin who was mentally retarded. She manifested no motor abnormalities, and findings from urine examination for amino acids were normal. The patient's father and three normal siblings also had normal urine amino acid patterns. Chromosomal studies were performed on the father, three normal siblings, and one affected patient (case 1). These studies showed enlargement of the short arm of a D-group chromosome in the father and both the clinically affected and unaffected siblings. The significance of this finding is unknown.

PATHOLOGICAL FINDINGS

The general autopsy examination of patient 2, performed four hours after death, showed focal and confluent areas of pulmonary consolidation due to acute bronchopneumonia. The gastrointestinal mucosa and submucosa were completely normal. Multiple sections of kidney, adrenal, thyroid, and pituitary glands were normal. Examination of the testes showed no evidence of gametogenesis, a reduced number of interstitial cells, and mild fibrosis. There was retarded epiphyseal closure of the long bones and metachromatic staining material in the subintimal media of the aorta.

The brain weighed 690 gm (average weight for age, 1,374 gm). It was diffusely atrophic with considerable enlargement of the subarachnoid space. The dura, leptomeninges, and blood vessels were normal except at the site of the recent biopsy. The cortical gyri were reduced in size but normal in configuration (Fig 4).

Section of the cerebrum showed diffuse and symmetric enlargement of the ventricular system. There was prominence of the cortical U fibers and a mild pallor of the underlying white matter most pronounced in the optic radiations. The cerebellar folia were atrophic. Section of the basal ganglia, brain stem, spinal cord, and nerve roots showed no additional abnormalities.

Paraffin-embedded complete coronal sections of the brain were stained with hematoxylin-eosin, Nissl, Woelke myelin, Bielchowsky, Sevier, phosphotungstic acid hematoxylin, and Holzer techniques.

Throughout the cerebral cortex there was a diffuse loss of neurons. This was most apparent in the occipital lobes (Fig 5). The neuronal loss was not associated with gliosis or distortion of the laminar cortical architecture. The remaining neurones appeared normal, although the cells were darker and smaller on Nissl stain than those of an age-matched control (Fig 6). The cerebral white matter appeared normal with the exception of the geniculocalcarine tracts (Fig 7). In this area, there was loss of axons and myelin, and intense gliosis. There was no evidence of active degenera-

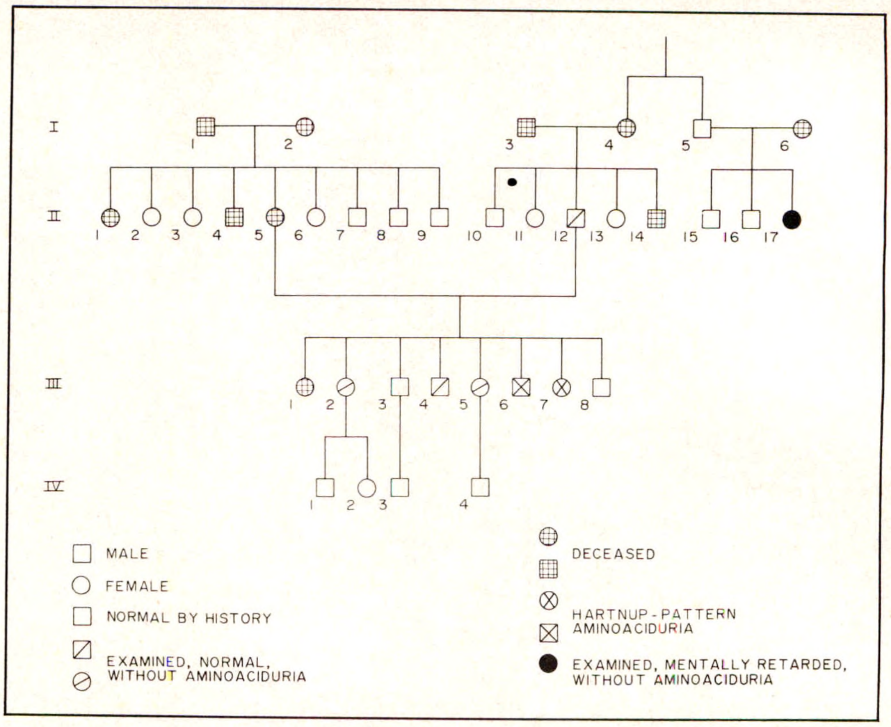
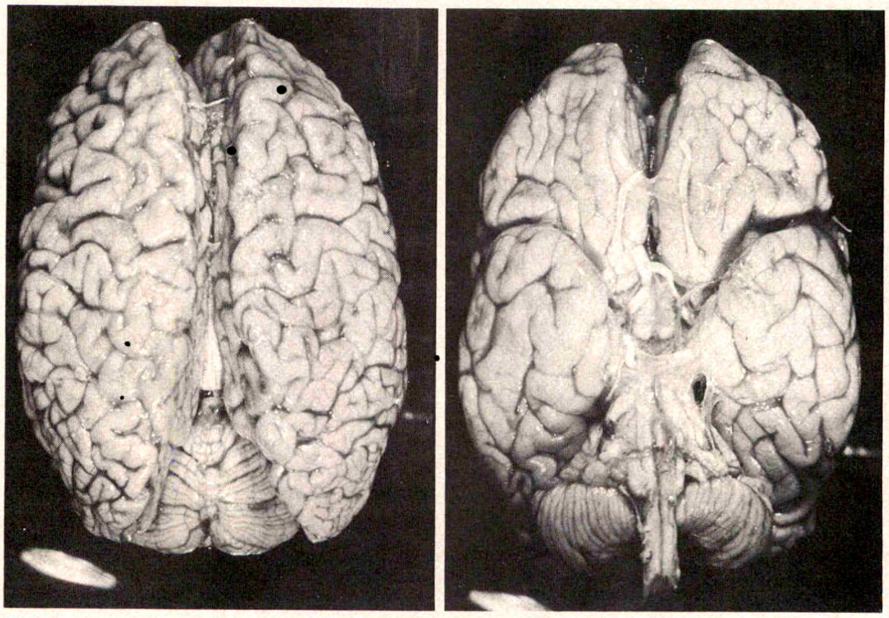

I
II
III
IV
MALE
FEMALE
NORMAL BY HISTORY
EXAMINED, NORMAL, WITHOUT AMINOACIDURIA
DECEASED
HARTNUP-PATTERN AMINOACIDURIA
EXAMINED, MENTALLY RETARDED, WITHOUT AMINOACIDURIA

Fig 3.—Pedigree of kindred. III-7, patient 1; III-6, patient 2; III-1, patient 3.

Fig 4.—Dorsal (left) and ventral (right) views of gross brain, showing diffuse atrophy (AFIP Neg 75-11976).



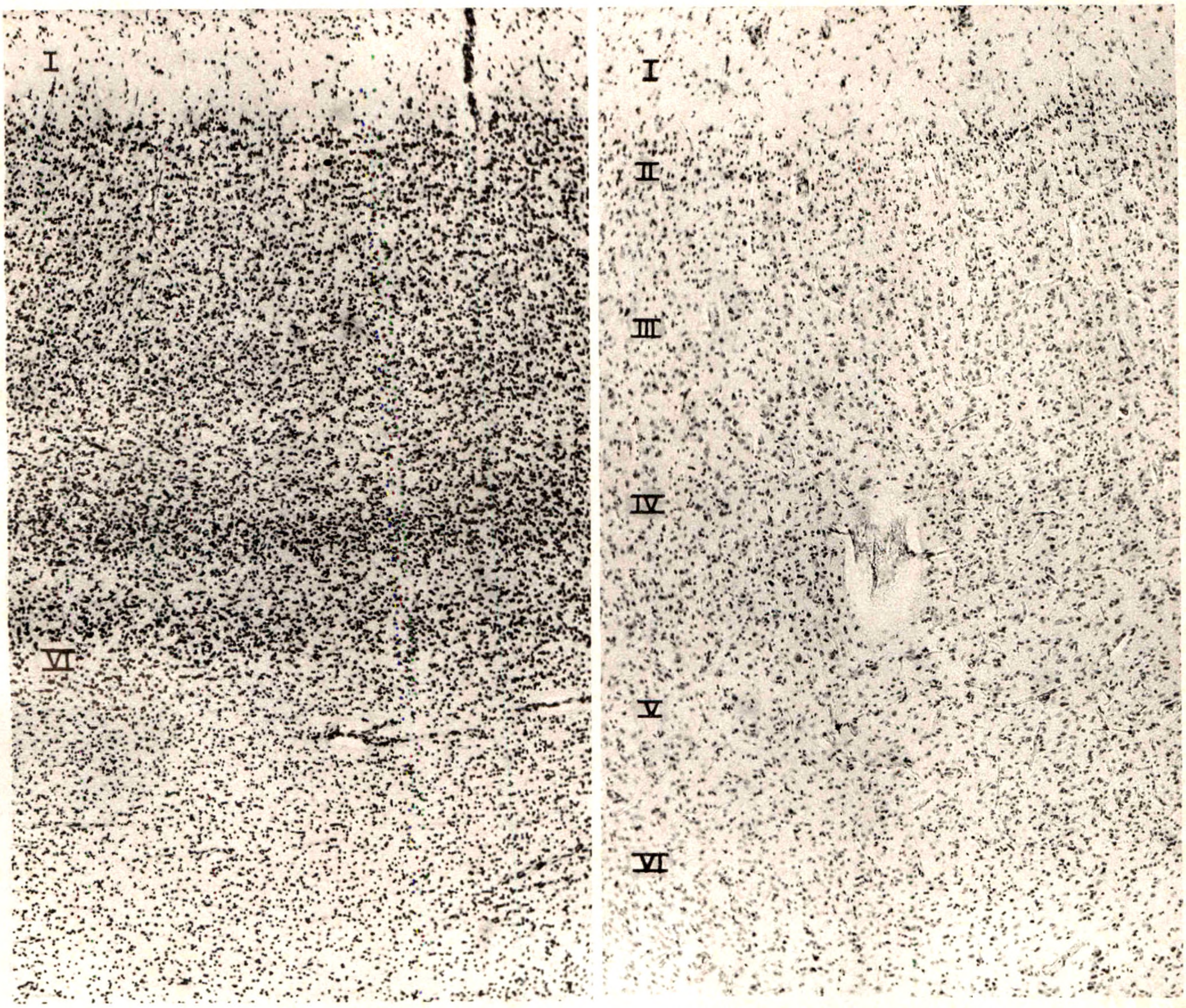


Fig 5.—Comparable areas of calcarine cortex from patient 2 (left) and normal, age-matched control (right). Roman numerals indicate approximate location of six laminae of cerebral cortex. Note considerable thinning of patient's cortex, with loss of neurons and condensation of remaining glial nuclei (Nissl stain, 20 μ thick, original magnification ×42, AFIP Neg 76-240).

tion in any area of the cerebral cortex.

The lateral geniculate nuclei were reduced in size. There was loss of their normal laminar architecture (Fig 8, top), neuronal loss (Fig 8, center), and intense gliosis (Fig 8, bottom). Many of the remaining neurons had shrunken dark nuclei and homogeneous basophilic cytoplasm with few discernible Nissl bodies. The optic nerves and tracts showed mild loss of axons and myelin.

Marked loss of Purkinje cells was evident in the cerebellum, and there was an associated prominence of Bergmann glia (Fig 9, top). Occasional degenerating Purkinje cells, axonal bodies, and dendritic swellings were present (Fig 9). The granular layer had thinned in proportion to the overall severe generalized atrophy.

Multiple sections of the basal ganglia, thalamic nuclei, subthalamic nuclei, hypothalamus, brain stem, spinal cord, and nerve roots showed no abnormalities.

MATERIALS AND METHODS

Quantitative amino acid analysis of plasma samples and 24-hour urine collections were performed by ion exchange chromatography on a Technicon TSM autoanalyzer. The spectrophotofluorometric method of Duggan and Udenfriend[33] was employed for plasma tryptophan determination.

Plasma samples were obtained at 8 AM, after an overnight fast, from patient 1 and four normal controls (aged 18 to 30 years). A 24-hour urine collection was also obtained from patient 1 and the normal controls. During this time, the patient was receiving 2,500 calories/day of liquid Meritene and the controls were on a regular diet.

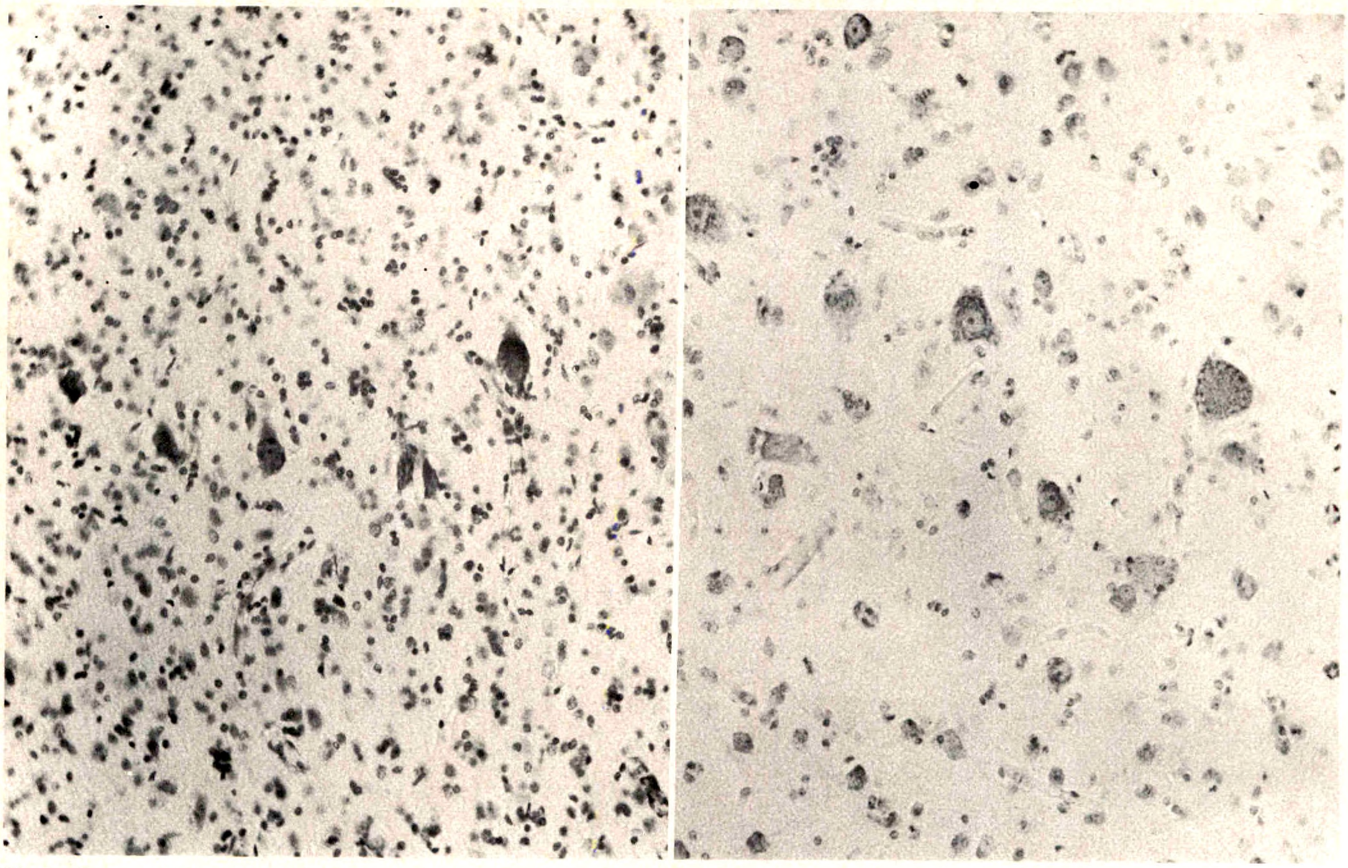
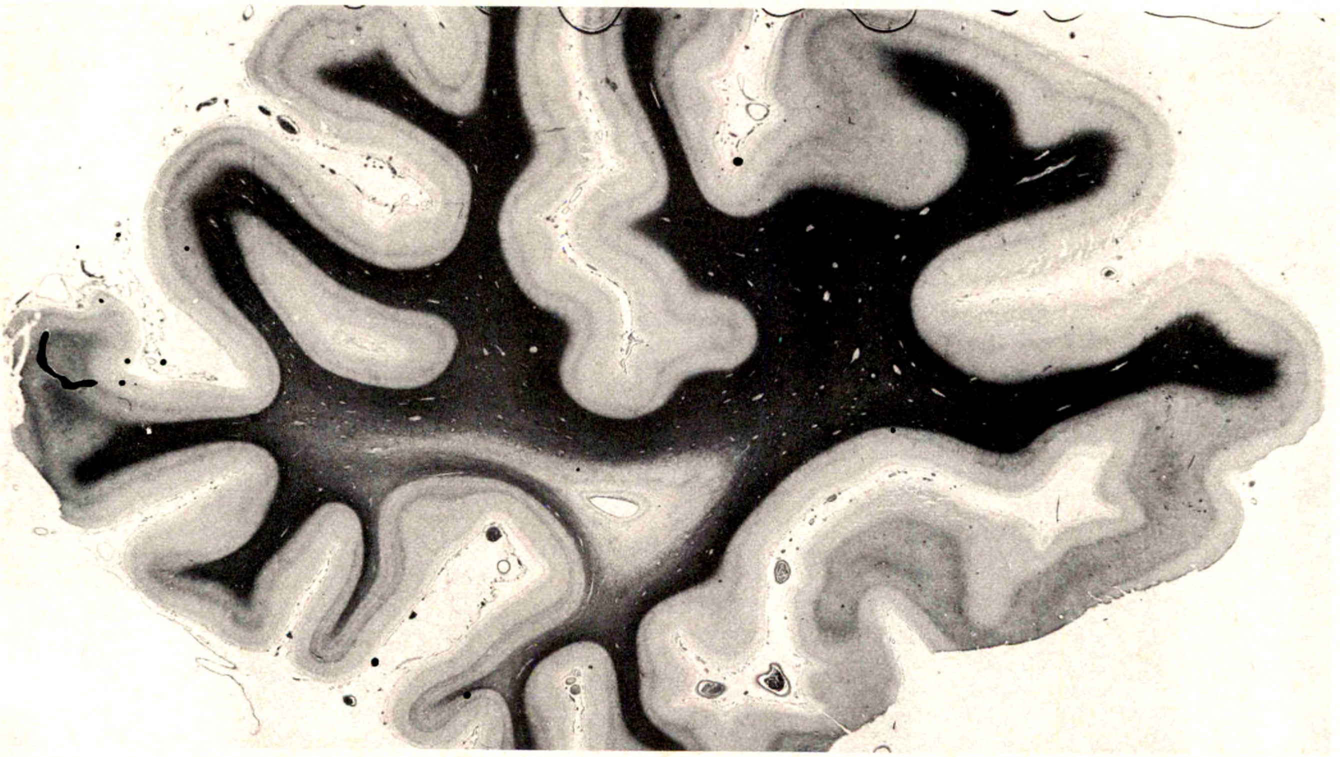


Fig 6.—Comparable areas of parietal cortex from patient 2 (left) and normal, age-matched control (right). Note relative loss of neurons in patient's cortex, with condensation of remaining elements. Neurons of patient 2 are darker and smaller than those of control (Nissl stain, 20μ thick, original magnification ×115, AFIP Neg 76-244).

Fig 7.—Coronal section of occipital lobe. Note absence of myelin staining in triangular area around occipital horn and adjacent to calcarine cortex, corresponding to geniculocalcarine tract. Diffuse cortical atrophy again evident (Woelke myelin stain, original magnification ×3, AFIP Neg 75-7193).



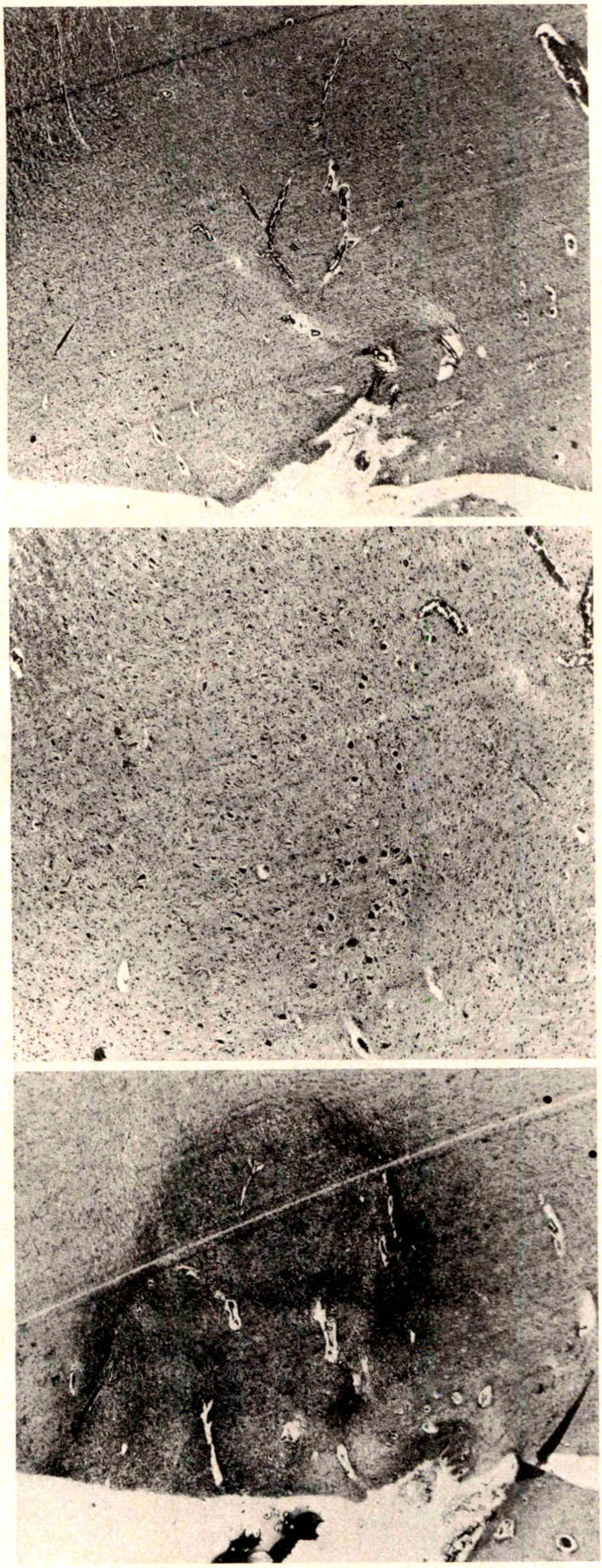


Fig 8.—Lateral geniculate nucleus. Top, Note atrophy of lateral geniculate nucleus, with loss of normal laminar architecture (hematoxylin-eosin, original magnification ×15). Center, Note severe diffuse loss of neurons. Remaining neurons have shrunken, dark appearance (hematoxylin-eosin, original magnification ×42). Bottom, Severe diffuse gliosis present in area confined to lateral geniculate nucleus (Holzer stain, original magnification ×15, AFIP Neg 76-235).

Fig 9.—Cerebellar cortex. Top, Severe loss of Purkinje cells is evident with staghorn masses in some of the remaining cells. Note prominence of Bergmann glia (hematoxylin-eosin, original magnification ×70). Bottom, Note shrunken Purkinje cell and several axonal bodies (Bielchowsky stain, original magnification ×265, WRAIR Neg 41478-2).

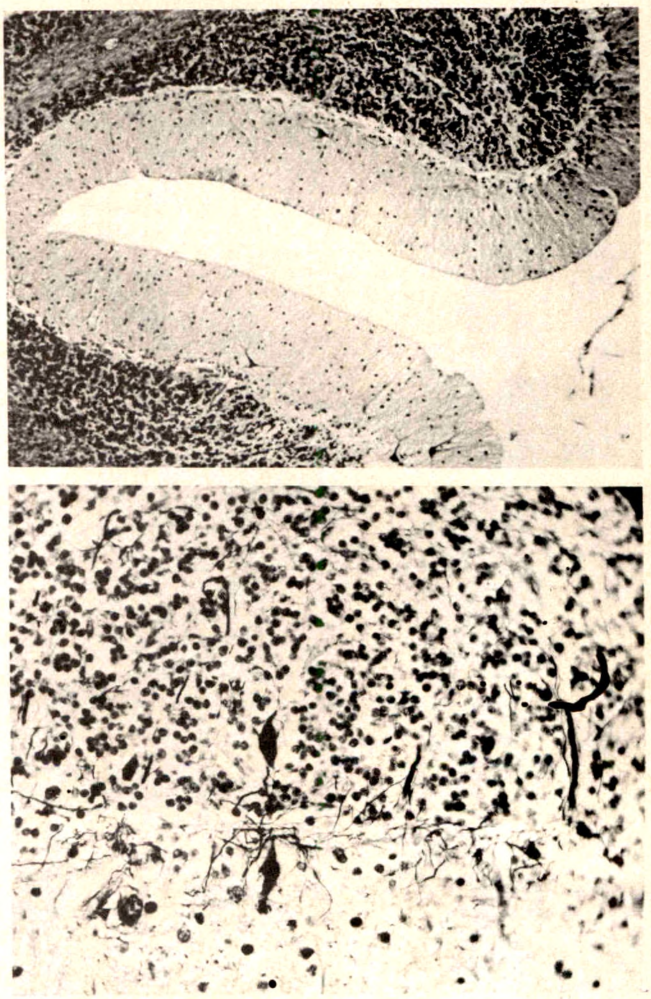


Table 1.—Urine Concentration of Amino Acids in Milligrams per 24 Hours

Amino Acid	Patient 1 July 1970	Patient 1 July 1971	Controls
Alanine	97	26	5-28
Serine	232	9	7-75
Threonine	99	17	10-41
Valine	17	4	1-6
Leucine	35	5	5-12
Isoleucine	69	2	2-21
Phenylalanine	374	14	7-14
Tyrosine	203	30	7-25
Histidine	1410	9	7-25
Methionine	24	3	ND-4*
Glutamine	455	34	10-99
Proline	ND	ND	ND
Hydroxyproline	ND	ND	ND
Glycine	359	53	37-136
Lysine	365	135	4-65
Arginine	8	ND	ND
Half cystine	113	ND	0-19
Glutamic acid	296	11	3-12

*ND indicates not detectable.

Oral amino acid loading studies were performed in patient 1 and two normal young adults (aged 25 and 30 years). After an overnight fast, the subjects were given 100 mg/kg of an amino acid in 300 ml of tap water. Blood specimens were obtained at zero, one, two, and four hours after oral administration. A 24-hour urine collection was obtained with each amino acid load. The loading studies were performed in July 1971 when the clinical status of patient 1 was stable and the urine amino acid pattern was normal.

The in vitro jejunal uptake of individual amino acids was studied by the method of Thier and co-workers.[34] Peroral jejunal biopsies were performed in patient 1. The biopsy specimens were obtained in July 1970 when the Hartnup-pattern aminoaciduria was present and in July 1971 when the urine amino acid pattern was normal. Control jejunal tissue was obtained at surgery from patients undergoing intestinal resection for ulcer disease. Each amino acid uptake was reported as the mean value obtained from three different biopsy specimens. Tissue samples weighing between .1 and 4 mg were incubated in Krebs-Ringer bicarbonate buffer containing ^{14}C-labeled amino acid at a concentration of 0.074 mM. Following a 45-minute aerobic incubation at 37 C, the radioactivity in the incubation medium and in the tissue was counted. The total tissue water and tissue extracellular fluid space was determined, and the tissue intracellular fluid space was calculated. These results were used to calculate the distribution ratio (counts per minute per milliliter in the intracellular fluid to counts per minute per milliliter in the incubation medium).

RESULTS

The concentrations of individual plasma amino acids were consistently within the control range. The concentrations of urine amino acids obtained from patient 1 in July 1970 were distinctly abnormal. Individual amino acids, with the notable exception of proline and hydroxyproline, were 3 to 30 times above the control range (Table 1). The urinary amino acid concentrations in a similar collection obtained in July 1971 were normal.

In the control subjects, the oral administration of an amino acid resulted in an increase in its plasma concentration during the first hour after ingestion and a gradual decrease between the second and fourth hours (Table 2). The general response and absolute magnitude of the plasma amino acid concentrations were similar to those of other controls performed in the same manner.[25] In patient 1 and controls, amino acid chromatograms performed on the urine obtained during the loading study showed no change from the baseline pattern.

In patient 1, the response to oral loading of glycine, proline, hydroxyproline, and basic amino acids (lysine and arginine) was similar to that in the control subjects. Normal and abnormal responses occurred after oral loading of neutral amino acids (alanine, serine, threonine, valine, leucine, isoleucine, phenylalanine, tryptophan, histidine, and methionine). The most abnormal response occurred after tryptophan loading. The peak plasma concentration occurred at two hours, and the one hour concentration was one third of the control value. The peak plasma concentration after oral loading of alanine, serine, and methionine was lower in the patient than the controls. The response after oral loading of threonine, valine, leucine, isoleucine, phenylalanine, and histidine was similar to the controls.

The results of the in vitro jejunal uptake studies (Table 3) were similar to those found after oral amino acid loading. The jejunal uptake of glycine, proline, and basic amino acids in patient 1 was similar to that in controls. Jejunal uptake studies of neutral amino acids resulted in normal and abnormal responses. The jejunal uptake of tryptophan, serine, methionine, valine, and leucine was significantly lower in patient 1 than controls. The uptake of threonine, phenylalanine, histidine, and tyrosine was not significantly different from controls. One year later, when the Hartnup-pattern aminoaciduria had disappeared, the uptake values for five amino acids were within one standard deviation of the mean values previously obtained.

COMMENT

The necessary condition for the diagnosis of Hartnup disease is the presence of Hartnup-pattern aminoaciduria.[1] This aminoaciduria was present in both patients 1 and 2. In addition, the fecal amino acid pattern and indoluria noted in these siblings were similar to those reported for the original Hartnup propositus.[4,5] Although the Hartnup-pattern aminoaciduria was described as contant in the original report,[1] review of the literature shows one patient in which the aminoaciduria completely disappeared[18] and another in which it decreased.[35]

Table 2.—Plasma Amino Acid Concentration at Zero, One, Two, and Four Hours After Amino Acid Loading (100 mg/kg)

		Plasma Concentration of Amino Acid, μmole/ml			
Amino Acid	**Subject**	**0 hr**	**1 hr**	**2 hr**	**4 hr**
L-alanine	Patient 1	0.30	0.61	0.46	0.25
	Controls (N = 2)	0.30-0.37	1.23-1.24	0.59-0.61	0.41-0.44
L-serine	Patient 1	0.17	0.52	0.32	0.26
	Controls (N = 2)	0.18-0.21	0.88-1.30	0.42-0.73	0.24-0.28
L-threonine	Patient 1	0.23	0.81	0.59	0.41
	Control	0.16	1.15	1.05	0.74
L-valine	Patient 1	0.41	2.08	1.53	0.85
	Control	0.31	1.81	1.66	1.15
L-leucine	Patient 1	0.19	0.91	0.30	0.22
	Control	0.14	1.09	0.51	0.20
	Controls from literature[25]	0.1-0.14	0.21-0.95	0.1-0.4	0.09-0.25
L-isoleucine	Patient 1	0.07	1.58	0.57	0.31
	Control	0.07	1.28	0.79	0.40
L-phenylalanine	Patient 1	0.09	0.49	0.31	0.16
	Control	0.05	0.66	0.28	0.12
	Controls from literature[25]	0.05-0.09	0.41-0.75	0.29-0.60	0.22-0.33
L-tryptophan	Patient 1	0.07	0.23	0.41	0.39
	Control	0.11	0.70	0.73	0.52
L-histidine	Patient 1	0.11	0.59	0.48	0.19
	Control	0.09	0.53	0.29	0.14
L-methionine	Patient 1	0.01	0.65	0.59	0.37
	Control	0.03	1.17	0.84	0.68
	Controls from literature[25]	0-0.05	0.85-1.18	0.70-1.12	0.58-0.75
L-proline	Patient 1	0.11	1.00	1.15	0.42
	Control	0.12	1.52	0.85	0.82
	Controls from literature[25]	0.1-0.2	0.78-0.95	0.50-0.75	0.40-0.70
L-hydroxyproline	Patient 1	0	0.58	0.37	0.15
	Control	0	0.61	0.48	0.38
L-glycine	Patient 1	0.26	1.68	0.56	0.29
	Control	0.18	2.00	0.93	0.48
L-lysine	Patient 1	0.24	0.57	0.39	0.35
	Control	0.24	0.86	0.79	0.54
	Controls from literature[25]	0.09-0.30	0.20-0.60	0.40-0.55	0.20-0.30
L-arginine	Patient 1	0.10	0.30	0.18	0.15
	Controls (N = 2)	0.10-0.11	0.23-0.46	0.20-0.29	0.13-0.15

The clinical course of our patients differed from that described by Baron et al[4] in that their symptoms were intermittently progressive and resulted in severe permanent neurological deficits. However, the types of neurological abnormalities noted were similar to those in the Hartnup propositus. Abnormalities in mentation, pyramidal tract signs, and cerebellar ataxia were common features. Choreoathetosis did not occur in the Hartnup propositus, and dermatological abnormalities did not occur in our patients.

With the exception of the amino acid transport defect, findings from functional and morphological studies of kidney and intestine were remarkably normal. The intestinal transport of lipids and sugars was normal, and histological examination of the intestinal mucosa indicated no structural abnormalities. The glomerular filtration rate and tubular reabsorption of phosphate were normal, and pathological examination of the kidneys showed no structural abnormalities. In addition, the renal and intestinal loss of amino acids did not result in abnormal concentrations of plasma amino acids or serum proteins.

The most striking clinical and pathological abnormalities were present in the central nervous system. Progressive dementia, optic atrophy, ataxia, and motor system abnormalities were the prominent clinical features. The progressive dementia was associated with loss of cortical substance as noted on serial pneumoencephalograms in patient 1. Neuropathological examination in patient 2 showed the cortical atrophy to be the end-stage of an unidentified process, which produced generalized and severe loss of neurons with condensation of remaining cortical elements.

The visual cortex, geniculocalcarine tracts, and lateral geniculate nuclei were the site of severe degenerative changes, which probably resulted in the blindness. Since optic atrophy can occur after bilateral damage to the occipital cortex,[36] it appears probable that the optic atrophy in this case is related to the degenerative changes described in the visual system.

The almost complete loss of neurons in the visual cortex may have produced a retrograde transneuronal degeneration of the lateral geniculate nuclei.[37,38] The combination of a diffuse neuronal lesion plus retrograde transneuronal degeneration may account for the unusual pathological features (disruption of laminar architecture and severe gliosis) found only in the lateral geniculate nuclei. The demonstration of loss of axons in addition to the loss of myelin and gliosis in the geniculocalcarine and optic tracts is consistent with a Wallerian degeneration rather than a demyelinating process.

The cerebellar ataxia and clumsiness noted clinically in patient 2 probably resulted from the severe Purkinje cell loss and cerebellar atrophy. No pathological abnormalities were found to explain the hyperre-

Table 3.—Amino Acid Uptake by Jejunal Mucosa in Patient 1 and Control Subjects

	Distribution Ratio* (Mean ± SD)			
	Patient 1			
Amino Acid	**July 1970†**	**July 1971‡**	**Controls, July 1970†**	***P*§**
L-serine	5.40 ± 0.94	...	8.37 ± 0.69	<.025
L-threonine	5.57 ± 1.57	...	6.43 ± 1.17	NS
L-valine.	25.66 ± 6.07	25.77	38.17 ± 14.84	<.025
L-leucine	26.52 ± 6.51	...	36.43 ± 2.09	<.025
L-phenylalanine	20.13 ± 6.91	...	27.77 ± 4.20	NS
L-tryptophan	10.72 ± 0.92	11.38	16.96 ± 3.80	<.001
L-methionine	24.77 ± 5.41	27.78	38.96 ± 18.25	<.01
L-histidine	5.97 ± 2.46	...	9.83 ± 0.29	NS
L-tyrosine	12.53 ± 5.05	...	19.70 ± 4.35	NS
L-proline	5.17 ± 0.98	4.64	6.60 ± 0.73	NS
L-glycine	5.00 ± 1.60	...	6.70 ± 2.35	NS
L-lysine	16.0 ± 5.8	...	11.49 ± 3.28	NS
L-arginine	15.43 ± 4.73	17.53	18.54 ± 3.17	NS

*Counts per minute per milliliter in intracellular fluid to counts per minute per milliliter in incubation medium.

†Three biopsy samples taken.

‡One biopsy sample taken.

§Student *t* test of 2 independent samples.

flexia and choreoathetosis, although these clinical signs may have resulted from the diffuse neuronal loss. The muscle wasting with type II atrophy was probably due to disuse.

The neuropathological findings noted in patient 2 are in striking contrast to the findings in inborn errors of amino acid metabolism, such as phenylketonuria,[39-41] maple syrup urine disease,[42,43] and arginosuccinic aciduria,[44] in which the abnormalities are predominantly confined to the cerebral white matter. Disorders of amino acid transport, such as iminoglycinuria and cystinuria, are not generally associated with neuropathological abnormalities.[2]

The clinical symptoms of Hartnup disease are similar to pellagra,[4] and nicotinic acid reverses the neurological abnormalities in both diseases when administered early in the clinical course.[4,14] Neuropathological studies of pellagra show a central chromatolysis and loss of neurons throughout the neuraxis without proliferation of glial elements.[45,46] Although the findings in patient 2 are consistent with the end-stage of this process, definition of the acute neuronal changes in Hartnup disease is necessary in order to compare the neuropathological abnormalities.

The transport studies in patient 1 indicate that many of the amino acids found in increased concentrations in the feces and urine are normally transported across the intestine when tested individually. The intestinal transport of tryptophan, serine, methionine, valine, and leucine was lower than that of controls, and abnormal excretion of these amino acids or their breakdown products was present in the urine or feces. Although abnormal excretion of glycine, basic amino acids, and other neutral amino acids was present in patient 1, the intestinal transport of these amino acids was not abnormal. The transport studies in patient 1 demonstrate the importance of directly measuring amino acid transport and suggest that speculations concerning transport defects based on excretion pattern may be seriously misleading.

The relationship between the transport defect and the neuropathological abnormalities present in Hartnup disease is unclear. Several factors indicate that the intestinal and renal transport defects are associated markers of the disease and not the sole causal factor producing the clinicopathological abnormalities. First, approximately one third of the patients with Hartnup-pattern aminoaciduria have no clinical abnormalities. Second, there appears to be adequate intake of amino acids from a combination of dipeptide and single amino acid absorption.[14,31] Third, the same intestinal transport defect was present during periods of clinical deterioration and stability in our patient. Therefore, it is suggestive that some patients with Hartnup-pattern aminoaciduria have an undefined pathological process in association with the renal and intestinal transport defect whose end effect is neuronal degeneration.

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HLA Haplotypes in Families With High Frequency of Multiple Sclerosis

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• Eight families from southern Sweden having two or more members with multiple sclerosis (MS) were typed for various alleles of the HLA system. The MS patients within each family shared one major histocompatibility system (MHS) haplotype, which was identical to the hitherto-described MS-associated haplotype A3B7Dw2 only in two of the families. Healthy relatives of MS patients were often found to carry the same haplotype as the affected members, which makes an estimate of the degree of penetrance of disease in individuals carrying the MS-predisposing MHS-linked gene possible.

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Siblings of patients with multiple sclerosis (MS) run approximately eight times higher a risk of MS developing than do the general population.[1,2] It has been proposed that this mostly depends on environmental factors. However, monozygotic twins have a higher concordance of MS than dizygotic twins,[3] and other studies of twins suggest that there may be "an autosomal recessive inheritance, but with reduced penetrance."[4]

Recently, an association has been noted between MS and the genetically determined histocompatibility antigens (HLA-A3 and HLA-B7),[5-7] but the association is weak compared with other disorders associated with the HLA system.[8] A stronger[9] but unverified (L. Stendahl, MD, H. Link, MD, E. Möller, MD, et al, unpublished data) correlation has been found between MS and the lymphocyte-defined (LD) antigen, HLA-Dw2 (7a), determined by the mixed lymphocyte culture (MLC) reaction.

These investigations have suggested that MS patients have a special "immune response" gene, localized in the chromosomal region, which contains the HLA genes. Its higher prevalence in individuals carrying either B7, Dw2, or both would be due to the well-established linkage disequilibrium of this haplotype,[10] and its presence would increase susceptibility to MS.

We have determined the prevalence of HLA-A, -B, -C, and -D products in eight families having two or more patients with MS. Since it is impossible to predict the incidence of the MS-predisposing gene directly, the only possibility of evaluation of the penetrance of the disease is to study the frequency of the MS-associated HLA haplotypes in families where MS has developed in one or more members.

PATIENTS

The study was made in families with two or more members who had MS according to the criteria given by Schumacher et al,[11] ie, objective neurological symptoms from two or more parts of the central nervous system, predominantly the white matter, occurring temporally in two or more episodes of relapsing attacks or in a slow or step-wise progression over a period of at least six months. The age at the onset of the disease must be between 10 and 50 years, with no other neurological disorder to explain the symptoms better than MS.

In southern Sweden, eight families were found in the area served by the University Hospital at Lund. About 500,000 people live within this area. The pedigrees of the families are shown in Fig 1 through 7. In these, the sexes and gestational years are also indicated.

Family A.—This family consists of seven siblings. Of these, No. 6, a woman born in 1942, has severe MS with bilateral visual disturbances after optic neuritis, and spastic paraparesis, ataxia, and permanent need of a wheelchair. Number 7, a man born in 1944, has had attacks with motor disturbances, all with good restitution. Both siblings have changes such as increased relative IgG concentration with an oligoclonal electrophoretic pattern in the cerebrospinal fluid (CSF). Another sibling, No. 3, a man born in 1934, had weakness of his left arm during three weeks in 1973 with complete recovery. His CSF was normal and the paresis was judged to be of peripheral origin. The parents of the seven siblings are dead, but a maternal aunt born in 1916 suffers from severe MS with dementia, ataxia, dysarthria, and spastic paraparesis. The siblings' maternal grandfather had a handicap of unknown cause requiring the use of a wheelchair.

Family B.—Two generations in this family were investigated. In the first generation there are three members, two of whom have MS. Their parents are dead, but from the childrens' description it seems probable that their mother had MS. In the first generation, the two affected members were born in 1917 and 1919, whereas their younger sister, born in 1925, is healthy. The two sick siblings have slight symptoms of motor disturbances in their legs. The onset of the disease was in 1934 and 1943, respectively. Earlier, they had experienced exacerbations of the disease with complete remissions. The seven children in the second investigated generation are all healthy, but still young (17 to 26 years old). In addition, the wives and husbands of the

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members of the first generation were investigated.

Family C.—Two sisters, born in 1925 and 1933, have MS. The eldest had a moderate but slowly progressing paraparesis; the other has bouts with complete remissions. Their mother is 73 years old and healthy. Each of the sisters has one daughter, 20 and 25 years old, respectively.

Family D.—This family consists of three members, and both the mother and son have MS. The mother has had slight symptoms for more than 20 years, whereas her son has had only two exacerbations of the disease with complete remission of symptoms.

Family E.—In the second investigated generation of this family, two of the three members have MS. The two affected members are men, born in 1931 and 1933. The eldest has a slowly progressing paraparesis, whereas the other has had several bouts of cranial nerve symptoms. Both brothers have increased oligoclonal IgG concentrations in CSF. Their sister, born in 1926, is healthy, but six years ago she experienced loss of sensibility on her right cheek lasting several weeks. She did not see a doctor and attributed the symptoms to concurrent dental work. The neurological examination is now normal, but she refuses lumbar puncture. The father of the three siblings is 69 years old and has painful osteoarthritis of his hips, with a diminished right quadriceps reflex. He has no other neurological symptoms and the present ones have appeared during these last years. Four persons in the third generation, 15 to 25 years old, have been examined and are all healthy. The wife of the MS patient born in 1933 has also been examined.

Family F.—This family had two affected members in the second generation. The youngest of the siblings, a woman born in 1940, has had mild MS since 1968, with exacerbations and almost complete remissions. She has a slight unsteadiness of gait. Her son, born in 1960, had optic neuritis with complete recovery of vision in 1973. However, he has diminished abdominal reflexes and increased, oligoclonal IgG concentration in CSF, as does his mother. His brother, his mother's siblings, and his maternal grandmother are healthy.

Family G.—In this family, two cousins have MS. Their parents are dead, but showed no neurological symptoms during life. Both of the MS patients are women; the eldest, born in 1919, has had MS since 1949, now with considerable weakness of her legs. The other patient was born in 1921, and has had MS since 1952. She is severely disabled, with dementia, ataxia, and paraparesis. A brother born in 1919 and the two children of the patients were examined and are healthy.

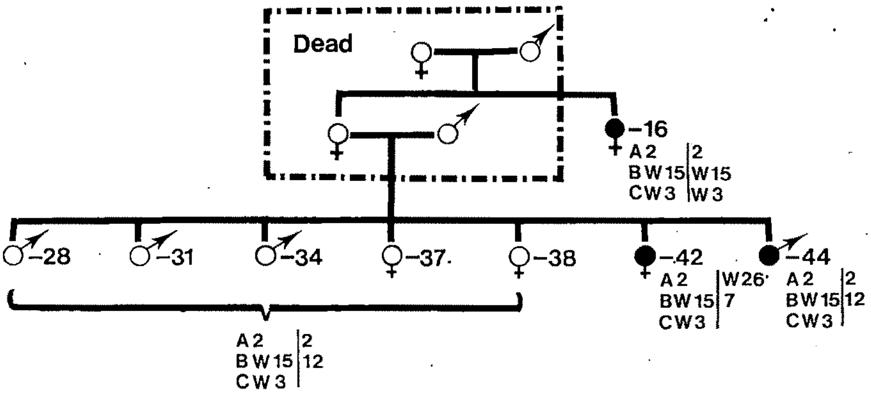

Fig 1.—Family A with three investigated MS patients (closed circles): two siblings in second generation and their aunt in first generation.

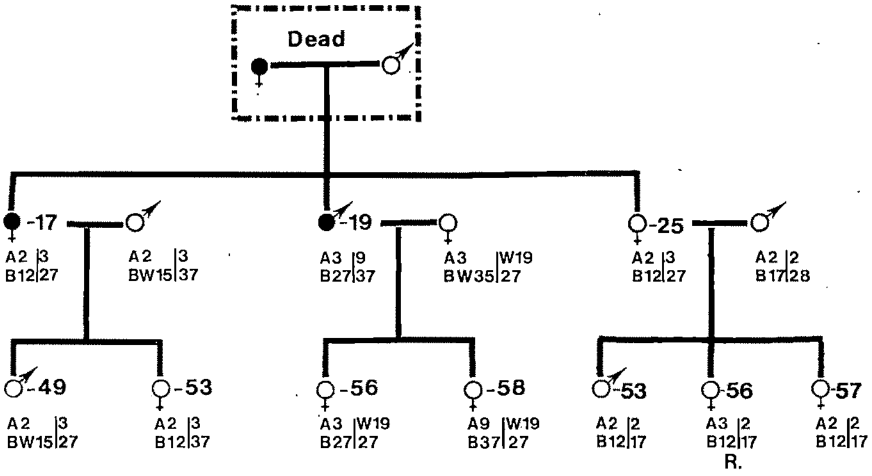

Fig 2.—Family B with two investigated MS siblings (closed circles) in second generation. Their mother, who is dead, probably had MS.

Family H.—Three members of this family were investigated. The daughter has MS with several earlier bouts, now in remission. Her father has a slowly progressing paraplegia with oligoclonal IgG concentration in CSF. The mother is healthy.

METHODS

HLA typing was performed according to the microcytotoxicity technique described by Kissmeyer-Nielsen and Kjerbye.[12] Lymphocytes from blood samples were purified by flotation on Ficoll-Isopaque.[13] Antisera against HLA-A, -B, and -C specificities were obtained.

Fresh or frozen lymphocyte suspensions were used for mixed lymphocyte culture. Cultures were performed in microplates containing 5×10^5 responder cells and 5×10^5 mitomycin-treated stimulator cells in a total volume of 0.2-ml medium (minimum essential medium containing Hepes buffer, 10% inactive human AB serum, and penicillin/streptomycin, 5.000 IU of each per milliliter). Tritiated thymidine (1 μCi; specific activity, 25 Ci/mmol) was added to all cultures on day 5 and incubation continued for 24 hours. Cultures were harvested with distilled water in an automatic cell harvester. The cells were absorbed onto glass fiber filters, which were dried at 60 C and thereafter transferred to scintillation vials containing a toluene-based scintillation fluid. Radioactivity was counted in a scintillation detector. Mixed lymphocyte culture results are expressed as counts per minute/culture ± SE. All cultures were performed in quadruplicate. In all experiments autologous controls with mitomycin-treated cells (A + Am) as well as mixtures of all cells, mitomycin-treated (Am + Bm, Am + Cm, etc) were performed.

Dw2 (LD-7a) "typing" cells were derived from three different LD-7a homozygous individuals, one of whom is the father in the first generation of family E; another is the female MS patient in the second generation of family H. The cells were characterized as Dw2 typing cells during the recent

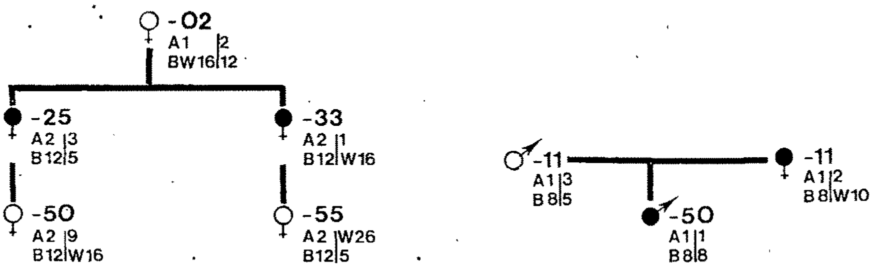

Fig 3.—Family C (left) with two investigated MS siblings (closed circles), and family D (right) with two investigated MS members (closed circles): mother and her son.

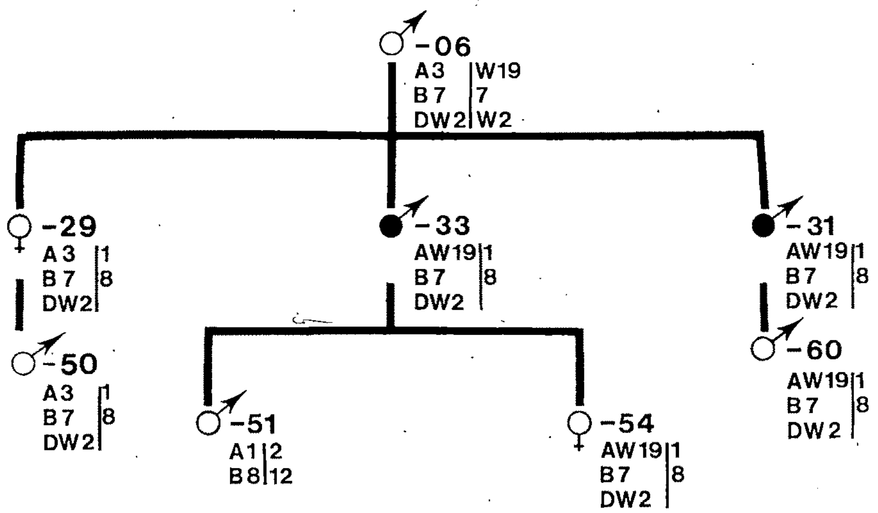

Fig 4.—Family E with two investigated MS siblings (closed circles) in second generation.

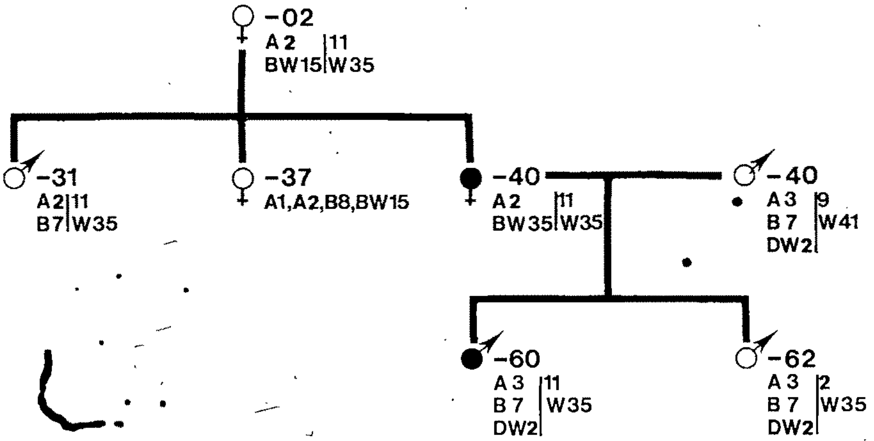

Fig 5.—Family F with two investigated MS members (closed circles): woman in second generation and her son in third generation.

histocompatibility workshop, and our reference cells have been described earlier.[14]

RESULTS

The HLA types and the presence of Dw2 as deduced from LD typing is given in the pedigrees (Fig 1 through 7).

Family A.—There is a notable homogenity in this family, as all of the siblings have the HLA phenotype 2,12,w15 except No. 6, who has 2,w26,7,w15. It is obvious that the mother of the seven children is also 2,w15 homozygous, since there are two different 2,w15 haplotypes in her offspring as shown by the MLC tests. Siblings 1, 3, and 4 were MLC-identical and were different from No. 2 and 7, who were mutually identical. Results with cells from No. 5 were doubtful. None of the members of this family has Dw2. Thus the two siblings with MS have different HLA genotypes. However, siblings 6 and 7 both inherited the haplotype A2Bw15Cw3. Mixed lymphocyte culture tests clearly show that there are two 2,w15 haplotypes in the family with different HLA-D alleles.

Sibling 6 in this family is incompatible with all the other siblings, and therefore one cannot definitely ascertain whatever of the 2,w15 haplotypes present in the two MS-afflicted children are identical. It can, however be ascertained that sibling 2, with no signs of the MS disease, is genotypically identical to No. 7, who has the disease.

Family B.—The affected members of this family have in common the HLA haplotype 3,27, and are Dw2 negative. If the MS gene is present on this haplotype, the healthy sister also carries the MS gene and thus the susceptibility to MS. She has not transferred this haplotype to her children, but two of the children of the affected members of the family have the haplotype and may carry the MS gene. Interestingly, one of the children of the healthy sister is an HLA recombinant, since she inherited HLA-A3 from her mother not with B27 on that haplotype but with B12 of the second haplotype. If she were to develop MS, it would indicate the position of the MS gene in the genome between the HLA-A and -B subregions.

Family C.—The MS patients in this family have the haplotype 2,12 in common; they are Dw2 negative. If the MS gene is coupled to 2,12, both daughters in the third generation would have this gene. However, their mother in the first generation may also have this gene, but has not shown any signs of MS.

Family D.—In this family the moth-

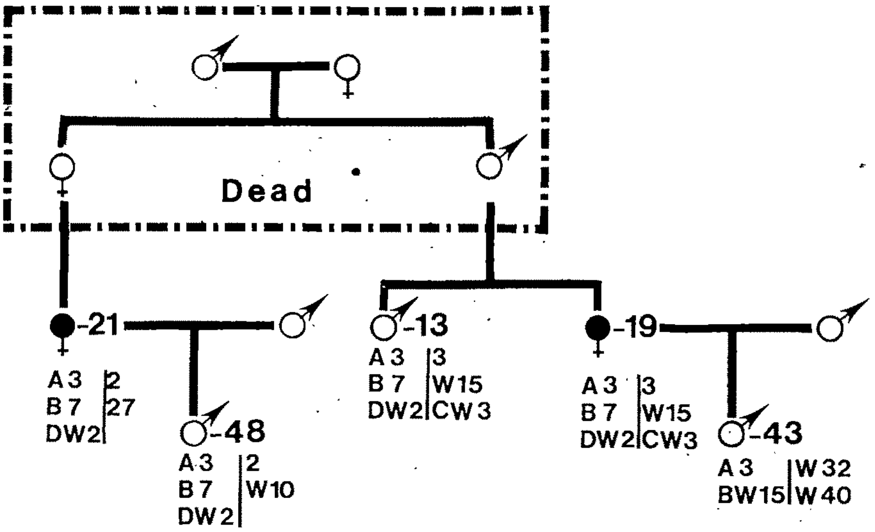

Fig 6.—Family G with two investigated cousins having MS (closed circles).

Haplotype Associated With MS Patients in Each Family

Family	MS-Associated Haplotype	No. of Unaffected Members*	
		With Haplotype	Without Haplotype
A	A2Bw15Cw3	1† (0)	4† (0)
B	A3B27	3 (1)	5 (0)
C	A2B12	3 (1)	0 (0)
D	A1B8	0 (0)	0 (0)
E	Aw19B7Dw2	3 (1)	3 (0)
F	A11Bw35	2 (1)	1‡ (0)
G	A3B7Dw2	2 (1)	1 (0)
H	A3B7Dw2	0 (0)	0 (0)

*Numbers in parentheses indicate unaffected family members older than 50 years of age.
†Results of the MLC test.
‡The sibling not born of the same parents was excluded.

er and her son, who have MS, have in common the haplotype 1,8. The son has also gotten a similar haplotype from his father, but is not HLA-D homozygous. Dw2 is not present in any of the members of this family. The MS gene may be present in the haplotype 1,8, which the mother and her son share, but not on the 1,8 haplotype received from the father.

Family E.—All the siblings in the second generation of this family have in common the haplotype 1,8, which is inherited from their mother. The MS gene may be coupled to this haplotype, but as MS has developed only in the two youngest brothers, it seems more reasonable to link the MS gene to the haplotype w19,7 containing Dw2, which both of them inherited from their father. In the third generation, two individuals may have received the MS gene and may have an increased susceptibility for MS. Since Dw2 has a high association to MS and the father in the first generation is Dw2 homozygous, he is the likely carrier of the MS predisposing gene.

Family F.—The three siblings in the second generation of this family have more than four HLA haplotypes, and cannot have the same father. Due to ethical considerations, their mother has not been asked about that. However, the two affected members share the haplotype 11,w35, which is not linked to Dw2. Dw2 is present on the paternal 3,7 haplotype carried by the third-generation children.

Family G.—In this family the two MS patients have the haplotype A3B7Dw2 in common, and it is very probable that the MS gene is present in this haplotype. The same haplotype is found in two other members, one of whom has reached such an age that onset of MS is highly improbable.

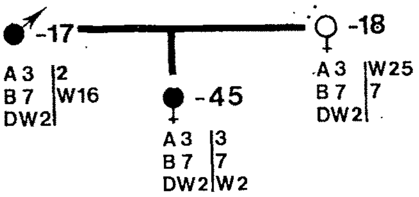

Fig 7.—Family H with two investigated MS members (closed circles): father and his daughter.

Family H.—The MS patient in the second generation of this family is homozygous for the haplotype A3B7Dw2. Her father has a spastic paraplegia, probably of the same pathogenesis as MS, whereas her mother is clinically healthy. It cannot be established whether the MS gene is present in both of these haplotypes or only in the parental haplotype.

COMMENT

The possible influence of genetic factors on a disease are best studied in families where several members have the disease. In MS, a certain association has been found between the disease and the antigens determined by the major histocompatibility system (MHS). A hypothetical MS gene may be proposed to be situated in the chromosomal region between the HLA-B and -D subregions. As it is impossible to directly study this gene, studies of families can give information of, for example, its genetic penetrance.

Recently, Alter et al[15] described the HLA antigens in ten families with two or more cases of MS in each family. Bird[16] determined these antigens in a family with MS in three generations, whereas the HLA antigens and the Dw2 (LD-7a) determinant have been analyzed only in one family.[8]

Our results are consistent with the findings in these twelve families in that the MS patients in each family had a special MHS haplotype in common. However, this haplotype was not identical in different families. In addition, close but healthy relatives to the MS patients were often found to carry the same haplotype as the affected members.

Alter et al[15] performed some statistical calculations concerning the penetrance of the suspected MS gene (called haplotype a). They found that this haplotype appeared in unaffected offspring, but there was a trend for a linkage between this haplotype and the MS patients that was statistically significant in one of three tests.

We have tried to apply these calculations to our eight families, but it is difficult for two reasons. First, we found differences in the MLC test between patients and healthy members with apparently identical HLA antigens (eg, in family A, six of seven siblings had identical HLA antigens, but the MLC test showed that they consisted of three different antigen groups). Second, the age of the unaffected members must be important for statistical calculations. As long as the healthy members were under 50 years of age, MS could still develop. In our families only five of the unaffected members were above this age, and all carried the suspected MS gene, whereas 23 members were younger (Table). Also, we do not know the ages of the members in the families presented earlier.

However, if we excluded these factors and only calculated with the HLA antigens in the MS patients and the unaffected members in the same way as the calculations were performed by Alter et al,[15] we found that 18 unaffected members had the suspected MS gene, and ten unaffected members lacked this haplotype. The difference was not significant ($\chi^2 = 2.28$, df_1, $P > .10$). If the results of the MLC test in family A were included, 14 unaffected members had the MS-suspected haplotype and 14 did not, which were the expected numbers. After excluding the two MS patients in each family who determined the MS-suspected haplotype, the remaining offspring in the second and third generations could be segregated into two groups: (1) members who had the suspected MS haplotype with MS or did not have either the haplotype or the disease (n = 15), and (2) those who had the haplotype without MS or had MS without the suspected MS gene (n = 11). If no linkage was assumed between these two groups, there should be 13 members in each group. Segregation analysis between the observed and the expected numbers showed no significant differences ($\chi^2 = 0.6$, df_1, $P > .40$). Only two of these 26 offspring were above the upper age limit of a possible MS onset. These calculations do not support the trend noticed by Alter et al[15] that lack of the suspected MS gene is associated with lack of MS. Instead, our findings show that the penetrance of the suspected MS gene must be very low. A large number of families is needed for calculation of the penetrance of the MS gene.

The main conclusion of the present family study is that there seems to be a common MHS gene for the MS patients in every family with the disease, but that this MS gene varies between different families. The genetic penetrance of this MS gene seems to be low, and cannot be calculated unless several families are analyzed where the unaffected members are above the upper age limit (50 years) for a possible MS onset. To be fully confident, the calculations should be done with patients who will be followed up until death and autopsy, as there have been reports of clinically silent MS cases only discovered by autopsy.[17,18] In addition, the families should not only be analyzed with respect to the HLA antigens, but also with the MLC test for determination of the Dw2 (LD-7a) factor.

These results make it difficult to predict MS from determination of the HLA antigens or the Dw2 determinant. The most frequent MS-associated haplotype, A3B7Dw2, was only connected with the suspected MS gene in two families, G and H, confirming the weak association between this haplotype and MS.[8] The Dw2 (LD-7a) determinant has been related to a more rapid progression of the MS disease.[9] In our 17 patients, we found no correlation between the course or the grade of disability and the MHS haplotype. In fact, the A3B7Dw2 homozygous patient in family H was free from symptoms after several years of the disease, whereas the most disabled patient was the woman in family A, born in 1918, who was A2Bw15 homozygous.

This work was supported by grants from the Swedish Multiple Sclerosis Society and the Swedish Medical Research Council. Lill Britt Anderson, Birgitta Hagström, and Berit Troedsson provided technical assistance. Antisera were obtained from the Scandia Transplant organization, Lierbyen, Norway. Mitomycin was obtained from the Sigma Chemical Corp, St Louis, and the minimum essential medium containing Hepes buffer, inactive human AB serum, and penicillin/streptomycin from Flow Lab, Solna, Sweden.

Nonproprietary Name and Trademark of Drug

Mitomycin—*Mitocin-C.*

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Cortical Neuronal Function During Ischemia

Effects of Occlusion of One Middle Cerebral Artery on Single-Unit Activity in Cats

Wolf-Dieter Heiss, MD; Toru Hayakawa, MD; Arthur G. Waltz, MD

• To assess the effects of ischemia on neuronal function, the action potentials of 261 individual cortical neurons were recorded extracellularly and related to regional cerebral blood flow (CBF) measured by hydrogen clearance in 19 cats, seven of which had the left middle cerebral artery occluded during a recording. The onset of ischemia could be associated with transient increases of activity, including "seizure discharges," as well as cessation of activity. No activity was noted at CBF less than 0.18 ml/gm/min; at higher (but ischemic) values for CBF, abnormal patterns of activity frequently were recorded. One neuron recovered function after cessation in association with an increase of CBF, indicating a potential for the restoration of function of ischemic neurons by effective therapeutic measures.

(*Arch Neurol* 33:813-820, 1976)

In experimental models of acute cerebral ischemia in animals, determinations of neurologic deficits and of electroencephalographic or electrocorticographic activity are imprecise; measurements of cortical-evoked potentials have proved useful,[1] but as yet no studies of individual neurons have been made. Therefore, we have measured the functional activity of 261 individual cortical neurons in 19 cats and related the activity to measurements of cerebral blood flow (CBF) made in the same regions at the same time; in seven cats, the functional activity of 162 neurons was measured before and/or during ischemia produced by occlusion of one middle cerebral artery (MCA).

METHODS

Preparation of Experimental Model

Seven unselected adult cats were anesthetized with phencyclidine hydrochloride, 1 mg/kg injected intramuscularly, and pentobarbital sodium, 20 mg/kg injected intraperitoneally. The head of each cat was immobilized in a head holder, the left MCA was exposed transorbitally, and an occlusion device was implanted.[2] In brief, the MCA was freed from its arachnoidal investiture and a silicone-treated 6-0 silk suture was looped carefully around it at its origin. The suture was manipulated into a single knot and its ends were passed outside the incision through a solid-ended tube-and-stylet that was apposed flush to the MCA and fixed to the wall of the orbit with epoxy cement. The optic foramen was sealed around the tube-and-stylet with Silastic sheeting, oxidized cellulose, and contact adhesive, and the orbit was filled with epoxy cement. The protruding ends of the stylet-and-tube and the suture were covered with a protective cap. After implantation of the devices the cats were allowed to recover from the anesthesia and the surgical procedures, and food and water were made available. Each cat was examined to be certain that there was no evidence of a neurologic deficit, leak of CSF, or intracranial infection related to the implantation.

Five to seven days after implantation of the occlusion devices, the cats were prepared for measurements of regional CBF and neuronal activity; 12 other cats without implanted occlusion devices were prepared in the same way. Nitrous oxide was chosen as the anesthetic agent because of its relative lack of influence on cerebral electrical activity[3]; for the initial surgical procedures, 80% nitrous oxide and 20% oxygen were given through an infant-size face mask after sedation with phencyclidine. Although the adequacy of nitrous oxide used alone as an anesthetic agent for cats has been questioned,[3] no movement of the cats was noted in response to the noxious stimulation of the surgical procedures.

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The trachea was cannulated with a T tube through a tracheostomy, and anesthesia was maintained. A polyethylene catheter was passed through a femoral artery into the abdominal aorta for the measurement of mean aortic blood pressure (MABP) with a strain gauge and a polygraph, and for the withdrawal of samples of arterial blood for measurements of Paco$_2$, Pao$_2$, and pH. A separate polyethylene catheter was passed through a femoral vein into the inferior vena cava for the injection of tubocurarine chloride for immobilization; an initial dose of 1.5 to 2.0 mg was supplemented by additional doses of 0.3 to 0.75 mg at intervals of 30 to 60 minutes. After immobilization, each cat was mechanically ventilated, and the head was placed in a stereotaxic machine. Wide thoracotomies were made bilaterally to minimize subsequent pulsation of the brain. The skull was removed over both cerebral hemispheres, the underlying dura was resected, and the exposed surfaces of the brain were protected with a pool of mineral oil warmed to 38 C. For subsequent measurements of regional CBF and neuronal activity, a mixture of 25% oxygen, sufficient carbon dioxide to maintain Paco$_2$ at 30 to 35 mm Hg (0% to 5%), hydrogen gas (H_2) as needed (0% to 3%), and nitrous oxide was used. Although the behavior of the cats could not be assessed because of paralysis with tubocurarine, 67% to 75% nitrous oxide was considered adequate as this concentration has been found to be a "potent analgesic and sedative" in cats.[3]

Measurement of Regional CBF

Regional CBF was measured by recording the appearance and clearance of H_2 administered by inhalation.[4,5] Recording electrodes were prepared from Teflon-coated wire composed of 90% platinum and 10% iridium, 125 μ in diameter. The Teflon was removed from the tip of a 3-cm length of the wire, exposing a conical segment approximately 1 mm long, which was platinized electrolytically in series with a 1-megohm resistance at −22 V in a 1% solution of platinum chloride. An ungrounded sintered silver-silver chloride indifferent electrode with large surface area[4] was inserted into the muscle of the back of each cat. To record CBF the platinized electrode was advanced into the cortex with a stereotaxic micromanipulator. A polarizing voltage of 400 mV, positive to the recording electrode, was applied; separate current sources, DC offsets, and differential inputs were used for each recording electrode.[4,5] After filtering and amplification, changes of electrical activity, directly and linearly proportional to changes of the amounts of H_2 present near the tips of the recording electrodes, were recorded on a polygraph.

At the time of measurement of CBF, H_2 was introduced into the tracheal cannula for 60 to 120 seconds, until an adequate deflection of the recording pen was observed on the polygraph. The flow of H_2 then was interrupted and its clearance from the brain was recorded. Subsequently, each curve of clearance was plotted on semilogarithmic paper to be certain that the rate of clearance was monoexponential. The CBF was calculated according to the equation CBF = $\lambda(0.693/T½)$, in which λ is the brain-blood partition coefficient for the indicator (=1 for H_2), 0.693 is the natural logarithm of 2, and T½ is the time required for the clearance curve to diminish to one-half the value recorded for it at the time of maximal clearance after interruption of inhalation and cessation of recirculation of H_2.[4] The CBF was expressed as milliliters per gram per minute.

Measurement of Neuronal Activity

Hollow glass microelectrodes with tips 1 to 3 μ in diameter were prepared, filled with a solution of 10% 3M potassium chloride and 90% 2M sodium chloride, and connected by silver wire and a shielded lead to an AC amplifier with separate ground and differential inputs. A stainless steel needle was placed in the exposed muscle of the neck of the cat as an indifferent electrode. The glass microelectrodes were advanced into the cortex with stereotaxic micromanipulators. The spontaneous activity of individual neurons, detected extracellularly and single-sidedly with filtration for an optimal pass at 1 kHz and a final gain of 10,000, was observed on a four-trace oscilloscope, listened to on loudspeakers, and recorded by FM on magnetic tape transported at 18.8 cm/sec. The recorded data were replayed through a custom-built analytic system utilizing a small computer to produce an interval histogram of 1,024 channels at 1 msec per channel. The number of action potentials per second was calculated from the number of intervals analyzed plus 1 divided by the time of analysis.

Simultaneous Recording of Neuronal Activity and Regional CBF

Simultaneous measurements of regional CBF and unitary activity were made by placing a platinum-iridium electrode in the posterior sylvian, middle ectosylvian, or posterior ectosylvian gyrus of one or both hemispheres to a depth of 1 mm, and advancing a glass microelectrode into the cortex within 1 mm of the recording electrode. When a suitable recording of unit activity was under way, hydrogen was introduced into the tracheostomy cannula and CBF was measured.

In five cats (No. 2, 9, 10, 11, and 12), MABP was changed by removal of blood through the arterial catheter, or by the intravenous infusion of a 10% solution of sodium nitroprusside or a 5% solution of phenylephrine hydrochloride. The potentials from 11 neurons were recorded at different levels of MABP.

In five cats (No. 1, 2, 3, 4, and 8), CBF was changed by changing Paco$_2$, either by increasing the rate of mechanical ventilation or by introducing additional amounts of carbon dioxide into the tracheostomy cannula. The potentials from 16 neurons were recorded at different values for CBF and Paco$_2$.

In each of the seven cats with occlusion devices implanted at the origin of the left MCA, measurements of CBF and neuronal activity were made before, during, and up to five hours after occlusion was accomplished by tightening the suture extending from the occlusion device.[2] In each cat, CBF and the activity of a neuron were recorded from the same region of the cortex just before, during, and just after MCA occlusion. In addition, activity was recorded from 21 other neurons in the left cerebral hemisphere before occlusion, from 106 neurons in the ischemic region of the left cerebral hemisphere after occlusion, and from 28 neurons in the right cerebral hemisphere after occlusion.

RESULTS

Effects of Changes of MABP and CBF

Changes of MABP did not result in changes of CBF, except when MABP decreased to less than 70 mm Hg or increased to greater than 160 mm Hg (Fig 1); thus, the normal regulatory processes that maintain CBF despite moderate changes of MABP ("autoregulation") were not impaired in the regions near the platinum-iridium electrodes. There were no consistent changes of the frequency of action potentials in association with changes of MABP, except in cats 2 and 10 after MABP decreased to very low levels and CBF also decreased (Fig 1). Increases of MABP and CBF were not associated with changes of frequency. CBF changed appropriately in response to changes of Paco$_2$; there were no consistent changes of the frequency of action potentials in association

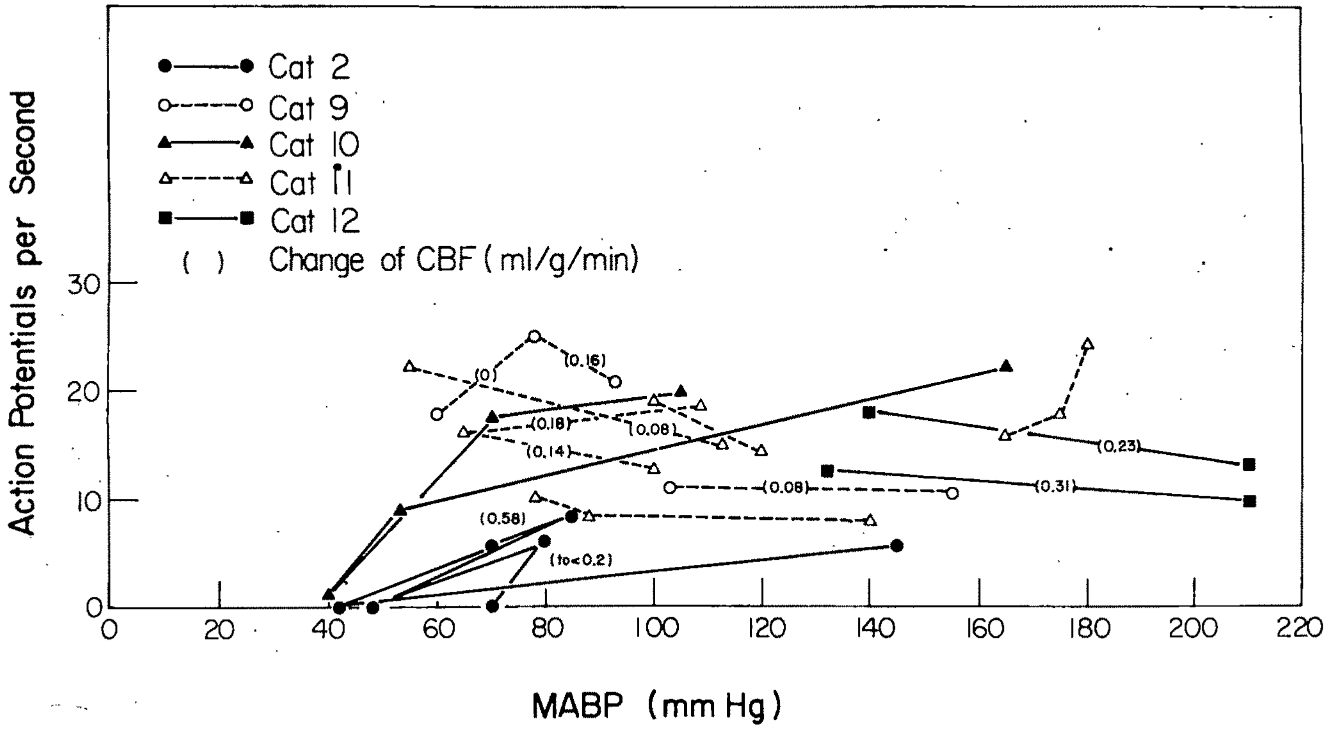

Fig 1.—Effects of changes of mean aortic blood pressure (MABP) on neuronal function and cerebral blood flow (CBF).

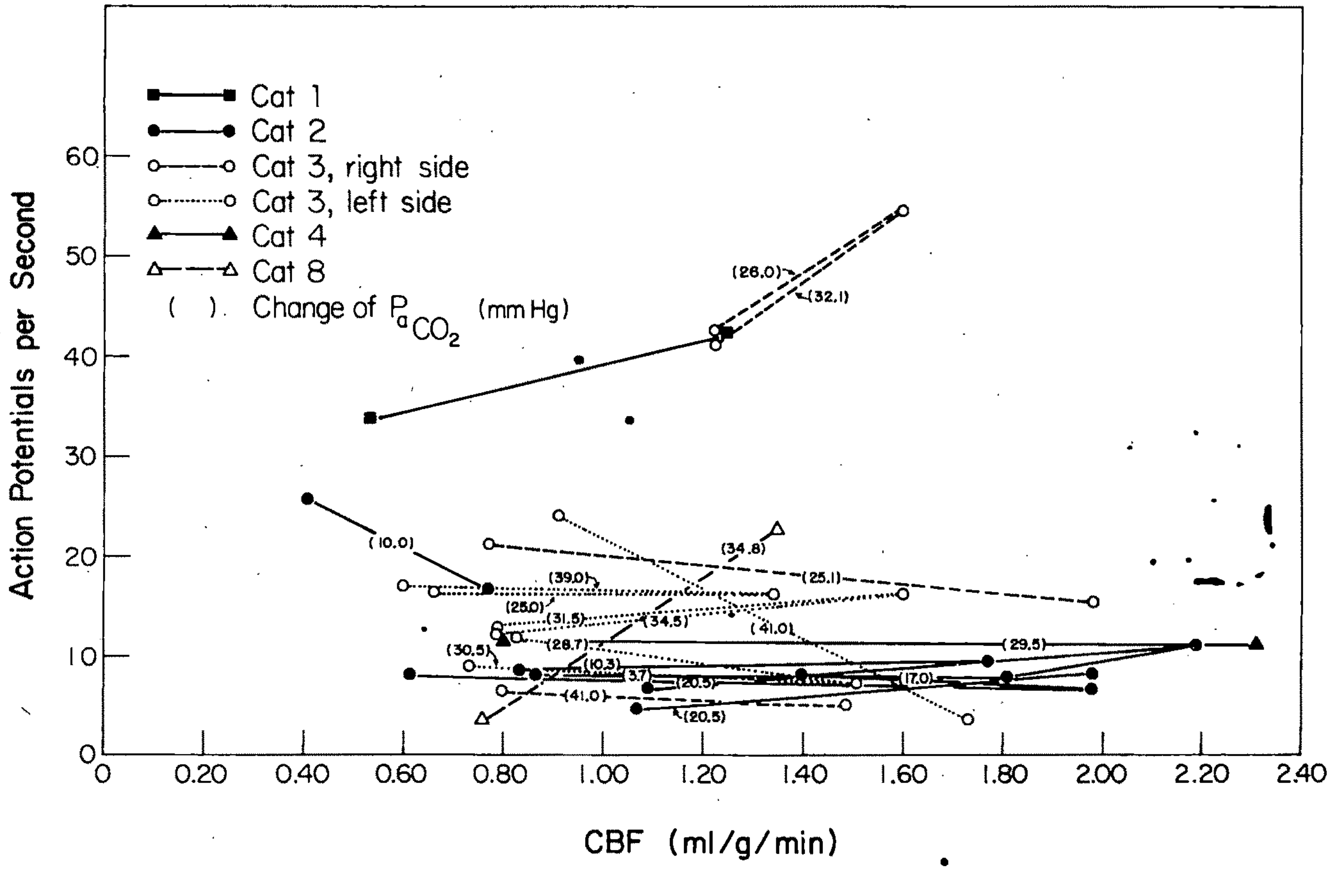

Fig 2.—Effects of changes of cerebral blood flow (CBF), caused by changes of Pa_{CO_2}, on neuronal function.

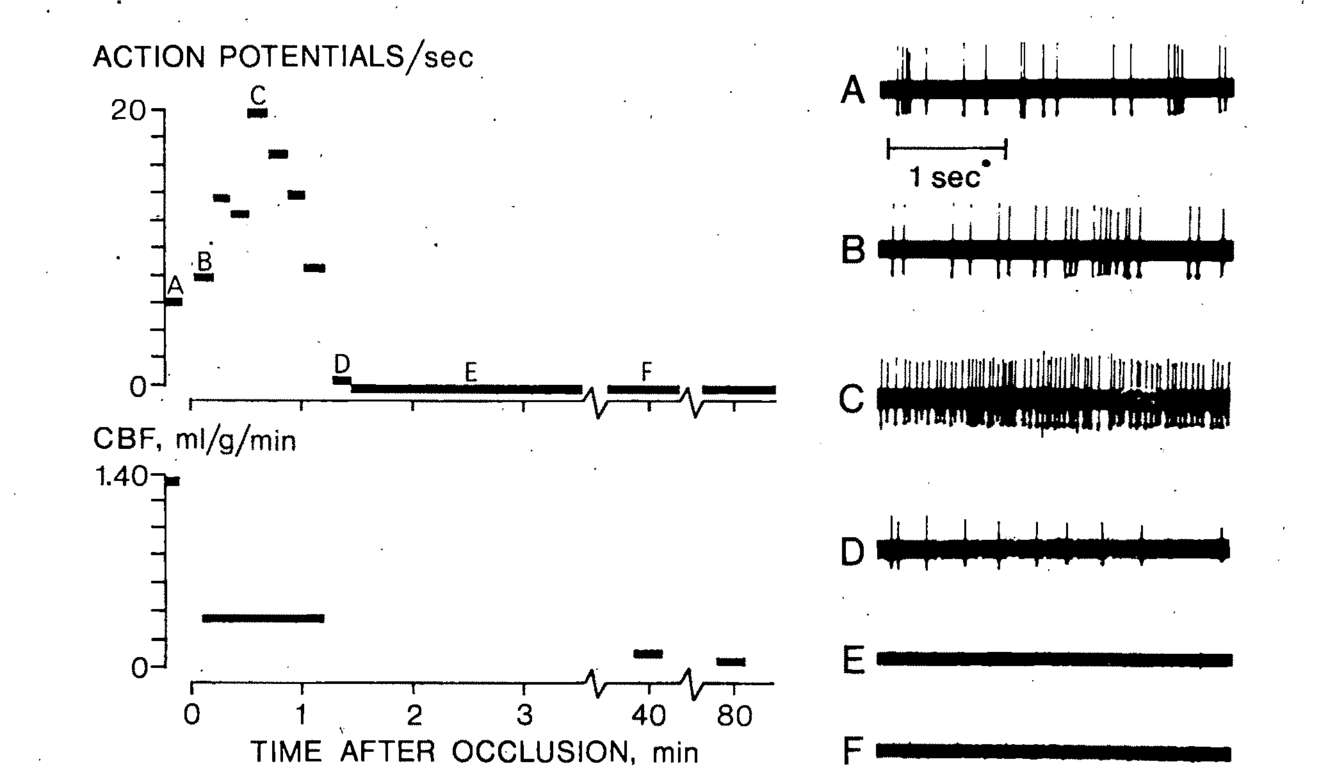

Fig 3.—Effect of middle cerebral artery occlusion on activity of a single cortical neuron in ischemic region of brain of cat 19. Note transient increase of frequency of action potentials followed by cessation of activity. Letters identify times at which the illustrated samples of neuronal activity were recorded.

with changes of Pa_{CO_2} and CBF at values for CBF above 0.60 ml/gm/min (Fig 2).

Effects of MCA Occlusion

In each of the seven cats with implanted occlusion devices, neuronal activity and CBF were normal, although variable, before MCA occlusion (Fig 3 through 5). Similarly, neuronal activity and CBF recorded from the right cerebral hemisphere after left MCA occlusion were within the expected variations of normal.

There were four patterns of change in the activity of the seven neurons that were studied before, at the time of, and after MCA occlusion. In three cats (No. 14, 15, and 16) there was an abrupt decrease of the frequency of the action potentials of the neuron under study, with cessation of activity from ten seconds to two minutes after occlusion. In two cats (No. 12 and 19) there was an abrupt but transient increase of the frequency of action potentials, followed by cessation of activity within two minutes of occlusion (Fig 3). In one cat (No. 17) prolonged, repetitive, high-frequency discharges followed an initial decrease of frequency; subsequently, infrequent individual potentials were recorded (Fig 4). In all these cats, CBF in the region of the glass microelectrodes remained very low after MCA occlusion, although in cat 17 CBF recovered to a value of 38.2 ml/gm/min. In the remaining cat (No. 18), an initial decrease of CBF after MCA occlusion to levels too low to calculate was accompanied by cessation of neuronal activity, but recovery of CBF to relatively normal values was accompanied by resumption of activity (Fig 5). The activity of the neuron was different after occlusion, in that the frequency of action potentials was greater and the pattern was more regular.

Abnormal patterns of activity were recorded from other neurons in the ischemic hemispheres of all seven cats after MCA occlusion; these abnormal patterns included bursts and regular firing at different frequencies (Fig 6). There were no consistent relationships between CBF and the patterns of neuronal activity, except that no neuronal activity whatever could be detected in regions with calculated values of CBF less than 0.18 ml/gm/min.

COMMENT

Methods for Measurement of CBF and Neuronal Activity

The measurement of regional CBF by the polarographic recording of the appearance and clearance of inhaled hydrogen gas has become a standard technique; the method used for this study was basically the same as that described by Pasztor and his associates.[4] Variability of values for CBF is great with all methods used for measurements,[5-7] and is related in part to the functional activity of the region for which CBF is being measured.[8-10] With decreasing sizes of electrodes sensitive to H_2, the sizes of the regions from which CBF is

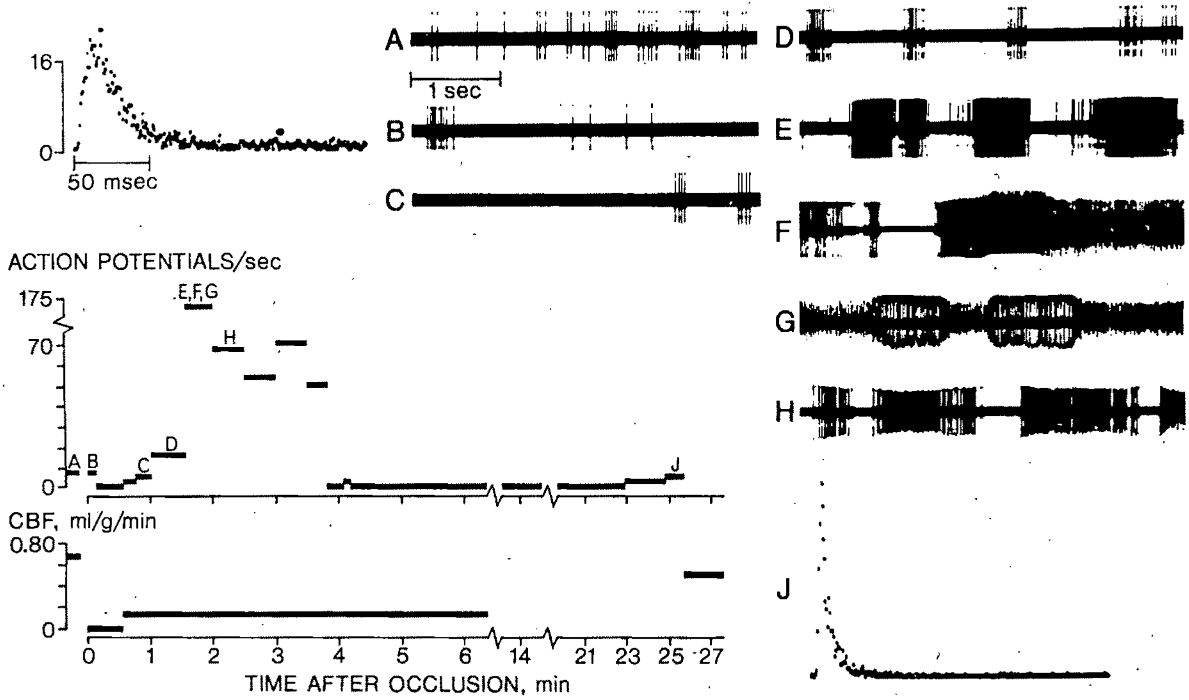

Fig 4.—Effect of middle cerebral artery occlusion on activity of a single cortical neuron in ischemic region of brain of cat 17. Note high-frequency repetitive discharges followed by cessation of activity, with resumption of very low-frequency activity after more than 20 minutes.

measured presumably also decrease, and variability of calculated CBF values becomes greater.[11,12] Variability also depends on the distance between the H_2 electrode and arterial and venous vessels.[11-13]

The sizes of the regions for which CBF was measured in the present study were unknown. It is possible that the sizes of the regions "seen" by an H_2 electrode may vary with CBF; the rate of diffusion of H_2 in brain tissue probably is much greater in regions where intercapillary distances are small and blood is flowing through the capillaries than in regions with aggregation of formed elements of blood, stagnation, or blockage of capillaries, such as can occur after MCA occlusion.[14] If the rate of diffusion through tissue is lessened, the influence of relatively distant regions on the H_2 electrode may be diminished. However, the monoexponential character of the curves of clearance of H_2 that were recorded suggests that the regions for which CBF was being measured were relatively homogenous. It is reasonable to assume that the values obtained for CBF reflected the actual values in the regions of the glass microelectrodes that were recording neuronal activity.

The method used for recording neuronal activity likewise is standard. A considerable amount of information about unitary activity in many different species has been obtained using the technique. In the present study, the activity that was recorded had patterns and interspike interval histograms that were the same as those described by others.[15-21] The relative stability of the discharge frequencies observed during changes of Pa_{CO_2} does not conflict with the findings of others of a depression of cortical unit activity at very high levels of Pa_{CO_2}[19,22]; the levels reached in the present study (maximum, 66 mm Hg) were adequate to cause changes of CBF but were much lower than the levels necessary for significant alterations of neuronal activity (approximately 150 mm Hg). Stability of discharge frequencies over a wide range of arterial blood pressures also has been observed for retinal neurons,[23] although no simultaneous measurements of retinal blood flow were made.

Immediate Effects of MCA Occlusion

The immediate effects of occlusion of one MCA on regional CBF measured by H_2 clearance already have been described.[5] The findings in the present study were similar to those of the previous study. In contrast to the reports of others[24,25] using different models of acute cerebral ischemia, CBF decreases immediately after MCA occlusion; subsequently, CBF may remain decreased, increase somewhat, or increase to hyperemic levels, depending on circumstances that are poorly understood at present.[5]

Continuous recording of single-unit activity may be interrupted by even slight movement of the animal or the recording microelectrode, because of separation of the electrode and the discharging cell. An interruption of activity by movement could be interpreted as cessation of activity due to ischemia if movement occurred during

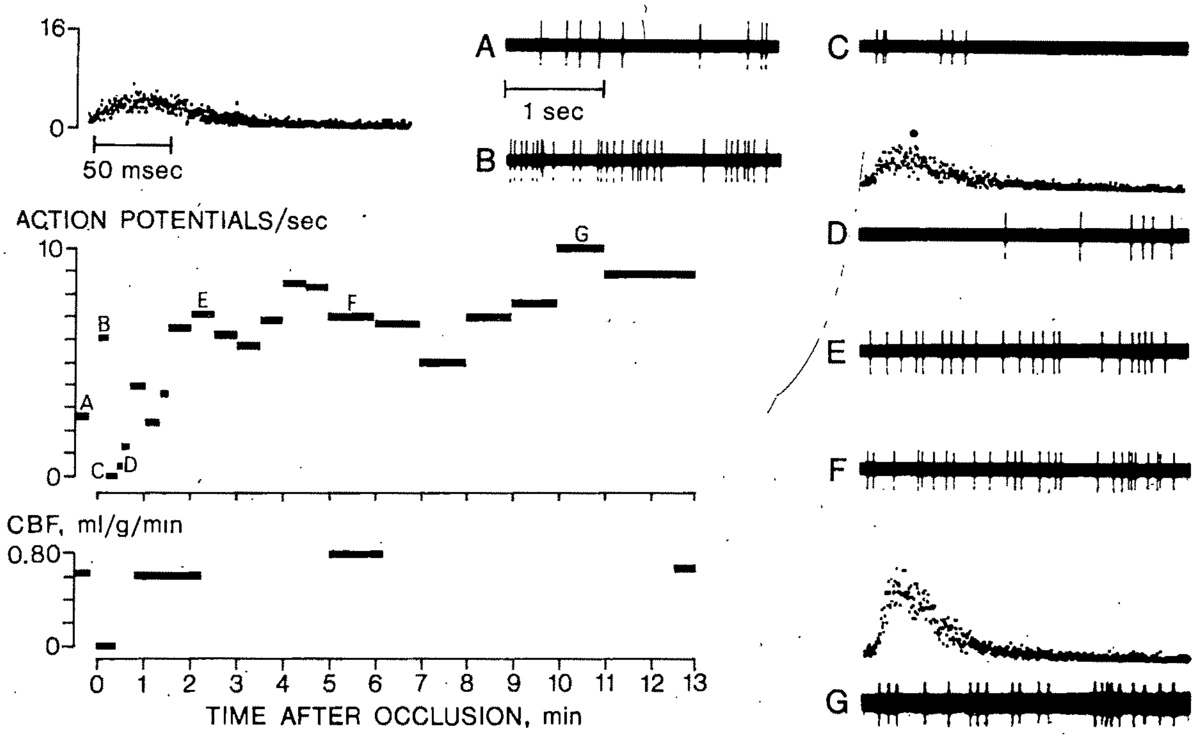

Fig 5.—Effect of middle cerebral artery occlusion on activity of a single cortical neuron in ischemic region of brain of cat 18. Note cessation of activity followed by recovery of cerebral blood flow (CBF) and resumption of activity with a different pattern.

MCA occlusion. In the present study, movements of the heads of the cats relative to the recording microelectrodes during MCA occlusion were prevented by fixing the heads and electrodes rigidly in a stereotaxic machine, and by employing a method for MCA occlusion that does not require any manipulation of the preparation other than gently pulling a suture placed at a distance from the electrodes. Thus, the effects of MCA occlusion on neuronal activity that were observed were most unlikely to have been related to movement.

It is noteworthy that changes of neuronal activity were found to occur within seconds of the onset of ischemia, an observation similar to those of others using anoxia or hypoxia.[16,17,26-29] Traditionally, four to five minutes of absent blood flow have been thought necessary for the development of irreversible impairment of neuronal function, as during cardiac arrest. However, in five cats used for the present study, neuronal function ceased within two minutes of the onset of ischemia. The cessation of function may not have been irreversible; in one cat (No. 17) there was subsequent recovery of neuronal activity when CBF increased spontaneously. This is strong evidence that reversible suppression of neuronal activity may be present for a variable period of time during ischemia; the implications will be discussed later.

Increases of the frequency of neuronal action potentials immediately after the onset of ischemia, such as were observed in three cats, may be related to hyperirritability induced by hypoxia[16,17,26-29] and hypoglycemia[30] or to an effect of ischemia on inhibitory neurons that influence the neuron under study. However, the finding of repetitive, high-frequency "seizure discharges" during ischemia suggests that hyperirritability, perhaps related to changes of membrane potentials,[22] is important in at least some instances. Clinically evident seizures are unusual in cats and in humans with acute nonembolic ischemic episodes[4,31]; however, the observations in cat 17 show that ischemia can give rise to seizures, presumably as long as some glucose and oxygen are available to maintain the abnormal neuronal activity. A massive neuronal discharge could be responsible in part for certain of the changes in neurotransmitters and other agents that have been reported for ischemic brain tissue.[32-35]

Implications for Treatment of Acute Ischemic Cerebral Infarcts

Studies of the relationships between CBF and electroencephalographic activity in humans undergoing carotid endarterectomy[36-39] and between CBF and evoked cortical potentials in baboons undergoing occlusion of one MCA[1] have shown a remarkable consistency: changes or disappearance of electrical activity occur when regional CBF decreases to approximately 0.17 to 0.20 ml/gm/min, and electrical activity recovers if CBF increases after a relatively short time. Moreover, the structural integrity of brain tissue appears to be

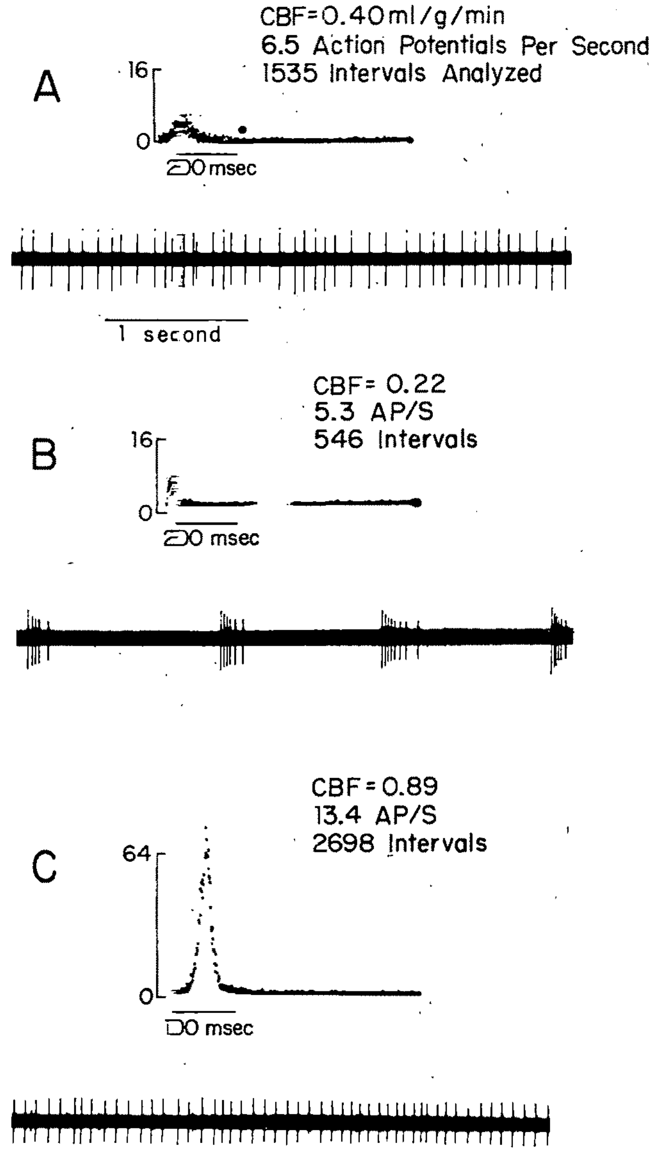

Fig 6.—Samples of abnormal patterns of neuronal activity recorded from ischemic regions of brains of cats with MCA occlusion.

affected only if CBF is less than about 0.20 ml/gm/min for an extended period.[40] In the present study no neuronal activity was detected in regions of brain with calculated CBF values less than 0.18 ml/gm/min; activity was present in regions with greater CBF values, although frequently the patterns of activity were abnormal.

Thus, the evidence available at present indicates that in normal brain there is a considerable reserve of CBF; neuronal function does not cease until a relatively low value for CBF is reached. Moreover, neurons that cease functioning at CBF less than about 0.20 ml/gm/min may resume functioning when CBF is greater than 0.20 ml/gm/min although still less than normal, as in cat 18. It is of particular interest that the critical value both for cessation of neuronal function and for structural integrity has been found to be roughly the same, and in three species: humans, baboons, and cats. These findings do not imply, however, that no transient or permanent neurologic deficits will develop unless CBF is less than about 0.20 ml/gm/min. The abnormal patterns of neuronal activity observed in regions of brain with higher (but ischemic) values for CBF might be found to be associated with neurologic deficits, when additional evidence becomes available.

The present study does not provide information about the maximal duration of a period of ischemia from which a neuron can recover. However, other studies in which neuronal function has been inferred from observations of neurologic deficits have indicated that recovery of function may be possible many hours after the onset of acute ischemia. In cats with MCA occlusion, spontaneous lessening of neurologic deficits may begin within several hours of occlusion and continue to the point that no neurologic deficit is detectable several days after the onset of ischemia.[2] Moreover, in anesthetized rhesus monkeys, an occluding device can be removed from one MCA many hours after occlusion with no resultant neurologic deficit.[41]

These experimental models are not precisely comparable to an acute stroke in humans; the influences of differing collateral circulation, effects of anesthesia, and other experimental maneuvers are not known with certainty. Nonetheless, even in humans there is indirect evidence that nonfunctioning regions of brain can remain viable for up to at least several hours.[42-44]

Thus, there appears to be a period of time after an acute ischemic stroke during which there is "functional paralysis" of neurons; if blood flow could be restored to ischemic regions, perhaps impaired neuronal function could be reversed. Unfortunately, immediate surgical procedures to restore cerebral blood flow to ischemic regions of brain have not met with unqualified success as yet. Restoration of blood flow may lead to worsening of ischemic cerebral edema,[5] with a resultant increase of neurologic disability. For neurovascular surgical procedures or other measures to be effective, it appears that they must be undertaken relatively shortly after the onset of ischemia, and that worsening of edema must be prevented. Nonetheless, the potential for restoration of function of ischemic neurons by effective therapeutic measures does exist.

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The Physiological Research Laboratory, Department of Neurosurgery, University of Minnesota, Minneapolis, developed the system used for analysis of recorded action potentials; James Bloedel, PhD, MD, and colleagues provided assistance and advice. David Debbins designed and built the equipment for recording action potentials and hydrogen clearance. Terry Hansen and Margaret M. Jordan provided technical assistance and advice.

Nonproprietary Names and Trademarks of Drugs

Phencyclidine hydrochloride—*Sernylan.*
Sodium nitroprusside—*Nipride.*

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Status Epilepticus in Immature Rats

Protective Effects of Glucose on Survival and Brain Development

Claude G. Wasterlain, MD, Thomas E. Duffy, PhD

• The role of glucose metabolism in alleviating the complications of status epilepticus (SE) was investigated in developing rats. Pretreatment with glucose reduced mortality from SE by 90% in rats under 1 week of age, 80% in 10-day-old rats, 50% in 15- to 20-day-olds, and not at all in adults. In 4-day-old animals, brain DNA synthesis during seizures, and, in survivors, brain weight, DNA, RNA, protein, and cholesterol contents at 7 days of age were reduced less in glucose-treated than in saline-treated littermates. In the saline group, seizures caused a progressive fall in brain glucose level but no fall in blood glucose level, suggesting that glucose transport from blood to brain could not keep pace with glycolytic demands. In glucose-treated rats, blood and brain glucose concentrations remained elevated throughout the convulsive period. There was no reduction of brain adenosine triphosphate levels in either group. Thus, the protection by glucose appears to be related to its role as a carbon source rather than an energy source. It is concluded that in immature animals, depletion of brain glucose can occur in the absence of hypoglycemia, and may be an important and potentially treatable complication of status epilepticus.

(*Arch Neurol* 33:821-827, 1976)

In 1942, Himwich et al[1] demonstrated that the administration of glucose prolonged the survival of rats in an atmosphere of nitrogen, the increase in survival being greater in immature animals. Since many of the metabolic and pathological effects of convulsive seizures resemble those of anoxia,[2] it seemed reasonable to expect that a similar protective effect of glucose might be obtained during status epilepticus. In fact, Lending et al,[3] in their study of the permeability of the immature blood-cerebrospinal fluid barrier, pretreated puppies with glucose in order to increase survival during repetitive seizures.

This report will demonstrate that pretreatment of immature rats with glucose reduces not only mortality but also the severity of brain damage caused by repeated seizures. As is the case with anoxia, the protection afforded by glucose during status epilepticus is strikingly age-dependent. Furthermore, the metabolic basis for this protective effect of glucose is suggested by the finding in 4-day-old rats that repeated seizures deplete brain glucose concentrations even in normoglycemic animals, and that glucose treatment prevents this fall in brain glucose content.

MATERIALS AND METHODS

Animals

Pregnant Wistar rats (CFN strain) were housed individually in a room with a 7 AM to 7 PM light cycle. After delivery, each litter was kept with its natural mother. At the

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age of 4 days, littermates were paired by sex and body weight (± 0.5 gm). In most experiments, both animals were subjected to intermittent seizures for two hours. One animal of each pair was injected intraperitoneally with 10% of its body weight of isotonic glucose solution (0.25 M) 30 minutes prior to the initiation of seizures. The paired control animal received 10% of its body weight of isotonic saline solution intraperitoneally. In some experiments, a third littermate, matched for sex and weight with the other two, received neither an injection nor seizures. In an additional series of experiments, saline-injected rats were compared with uninjected paired littermates subjected to the same seizure regimen. To minimize the effects of circadian variations, all experiments were carried out between the hours of 1 and 4 PM.

Seizures

Status epilepticus was induced either by a single injection of bicuculline (10 mg/kg intraperitoneally, dissolved in 0.1N hydrochloric acid and brought to pH 7 immediately prior to injection), or by intermittent exposure to the volatile convulsant, flurothyl. Flurothyl-induced seizures in immature rats were induced by placing the animals in a 1-liter jar that was partially immersed in a 36 C water bath; every five minutes, flurothyl was injected against the inner wall of the jar in volumes of 50μl for the first 90 minutes of the experiment, and 100μl thereafter. For adult animals, a 5-liter jar was used, and the dose of flurothyl increased proportionately. Once the convulsant was added to the jar, the lid was replaced for four minutes and then removed for one minute. The oxygen content of the jar, measured with an oxygen-sensitive electrode, remained close to that of room air throughout the experiment.

Chemical Methods

For developmental studies, rats were killed by decapitation with a guillotine. The entire forebrain rostral to an intercollicular cut (minus olfactory lobes) was removed and blotted on acid-washed filter paper. The brains were weighed, immersed-frozen in liquid nitrogen, and stored at −80 C. Prior to analysis, the frozen brains were homogenized in 10 volumes of 0.1M phosphate buffer (pH 7.2); RNA content was determined on the homogenates by a modified Schmidt-Thannhauser procedure,[4] DNA by the method of Webb and Levy,[5] protein according to Lowry et al,[6] and cholesterol by the technique of Zlatkis et al.[7] Since the DNA content of all diploid cells of a species is the same,[8] cell numbers were estimated from brain DNA contents on the assumption that the small percentage of polyploid brain cells[9,10] was not greatly altered by the experimental procedures.

For metabolic studies, rats were killed by immersion with vigorous agitation in liquid nitrogen. Frozen specimens were stored at −80 C until they could be prepared for analysis. Forebrains were dissected in a −20 C room and powdered under liquid nitrogen. A weighed portion of the frozen powder (approximately 100 mg) was then layered over three volumes of frozen 3.0M perchloric acid and homogenized in an alcohol-dry ice bath kept at −10 C. Ten volumes of cold 5-mM edetic acid were added, and the entire mixture rehomogenized and centrifuged at 5,000 g for 30 minutes at 0 C. The supernatant fluids were neutralized with 2.0M potassium bicarbonate to pH 6.5 to 6.8. Precipitated potassium perchlorate was removed by centrifugation; the supernatant fluids were assayed for adenosine triphosphate (ATP), glucose, and lactate by enzymatic, fluorometric methods. Glucose and ATP levels were measured with the conditions of Lowry and Passonneau[11]; lactate content was determined as described by Vannucci and Duffy.[12]

Arterial blood (20μl), obtained by cardiac puncture 30 seconds prior to killing the animals, was acidified with 300μl of 0.5M perchloric acid at 0 to 4 C. Neutralized extracts were prepared and analyzed for glucose in the manner described for brain samples.

Estimation of DNA Synthesis

For measurements of DNA synthesis during status epilepticus, 4-day-old rats were injected with [methyl-^{3}H]thymidine (5μCi/gm, intraperitoneally) 40 minutes after the onset of repeated, flurothyl-induced seizures. At 10, 20, or 30 minutes after the injection, the animals were decapitated. The brains were removed, weighed, and homogenized in 10 volumes of 0.1M phosphate buffer (pH 7.4). Aliquots of the brain homogenates were precipitated with 3 volumes of 0.6M perchloric acid at 0 C and centrifuged. Aliquots of the supernatant fluids were suspended in dioxane-based scintillation fluid (Instagel) and counted in a liquid scintillation spectrometer to determine the radioactivity of brain thymidine. The pellets (containing the precipitated DNA) were washed twice with 0.2M perchloric acid, resuspended in 0.1M potassium hydroxide, and incubated for 60 minutes at 37 C to hydrolyze RNA; the mixtures were then chilled in an ice bath and acidified with 2.5 volumes of 1.2M trichloroacetic acid (ice-cold). The precipitate was washed twice with 0.2M trichloroacetic acid, resuspended in 5 ml of 0.6M trichloroacetic acid, and heated at 90 C for one hour to hydrolyze the DNA into monodeoxyribonucleotides. The radioactivity of the hydrolysate was determined in dioxane-based scintillation fluid, and the deoxyribonucleotide concentration was assayed with *p*-nitrophenylhydrazine.[5]

Control and experimental values were compared by means of the Student *t* test.

RESULTS

Age-Dependent Effects of Glucose Load

Pretreatment of immature rats with glucose increased their survival during flurothyl-induced status epilepticus, the protection by glucose being most striking among the younger age groups (Fig 1). While the number of seizures varied with the age of the animals (older rats died more quickly), there were no differences in intensity or duration of the seizures between glucose-treated or saline-treated rats in any particular age group. At 1 day of age, ten of 29 saline-injected and only one of 29 glucose-injected rats died (seizures lasted three hours). Among 4-day-old rats, 42 of 103 saline-treated and two of 103 glucose-treated animals died during the course of status epilepticus (two hours). Among 10-day-olds, 13 of 16 saline-injected rats and two of 16 glucose-injected rats died. Among 20-day-olds, 11 of 13 saline-treated and seven of 13 glucose-treated animals died during repeated seizures. In adult rats, mean survival was 65 minutes in the saline-treated group and 72 minutes in the glucose-treated group; the difference in survival time was not significant. Mortality was 100% in both groups, precluding comparison, and a second experiment was therefore devised.

Adult rats were injected with glucose or saline, and 30 minutes later were subjected to supramaximal electroshocks every 30 seconds through ear clips; the animals responded to every electrical stimulus by a full tonic-clonic convulsion. The number of seizures sufficient to kill 50% of the animals (LD_{50}) and the mean survival time both tended to be higher in the glucose-treated rats (Table 1), but neither difference was significant. The LD_{100} was actually greater in saline-treated rats, but this reflected prolonged survival of a single saline-treated animal. These data indicate that glucose administration, which reduced mortality from flurothyl-induced status epilepticus by as much as 90% during the first week of life, afforded adult rats little, if any, protection from repeated chemical (Fig 1) or electrical (Table 1) seizures.

Effect of Saline Load

It was conceivable that the difference in mortality between saline- and glucose-injected immature rats during seizures represented simply an adverse effect of saline and not protection by glucose. To test this possibility, the mortality of paired uninjected and saline-injected 4-day-old rats was compared during flurothyl-induced status epilepticus lasting for two hours. In each group, 11 of 20 rats (45%) died, indicating that saline pretreatment had little or no effect on mortality from repeated seizures.

Serum Osmolarities During Status Epilepticus

The lower mortality during seizures of glucose-treated animals compared with saline-treated rats was unrelated to serum osmolarity (Table 2). In both saline- and glucose-treated 4-day-old rats, serum osmolarity tended to increase during status epilepticus, but there were no significant differences between saline- and glucose-injected animals at any time.

Seizures Induced With Bicuculline

Glucose pretreatment also protected immature rats from the mortality of status epilepticus induced by other convulsive agents. Thirty-five pairs of 4-day-old rats were subjected to bicuculline seizures (10 mg/kg, intraperitoneally) 30 minutes after glucose or saline administration. This dose of bicuculline produced repeated tonic-clonic seizures lasting from 60 to 90 minutes. Mortality was 71.4% in saline-injected rats. It was signifi-

Table 1.—Glucose Treatment and Mortality From Repeated Electroshock-Induced Seizures in Young Adult Rats*

	Saline-Treated (N = 14)	**Glucose-Treated (N = 14)**
Mean survival, min	34.7 ± 5.8	38.4 ± 3.0
LD_{50}, min†	31	39
LD_{100}, min†	60	50

*Animals were injected with either isotonic saline or glucose, and 30 minutes later were subjected to repeated electrically-induced (150 v, ac, 1-second duration) seizures every 30 seconds. There were no significant differences ($P > .05$) between the two groups.

†LD_{50} indicates number of seizures sufficient to kill 50% of the animals, LD_{100}, number of seizures sufficient to kill all the animals.

Table 2.—Serum Osmolarities During Flurothyl-Induced Status Epilepticus in 4-day-old Rats*

Time After Injection, min	**Saline-Injected**	**Glucose-Injected**	**Uninjected Controls**
0	298	290	294
30	302	305	
60	304	306	
120	307	307	

*Animals were injected with either isotonic glucose or saline, and 30 minutes later subjected to intermittent seizures with flurothyl. Each value is the mean of three determinations of freezing point depression; sera from three animals were pooled for each measurement. All values expressed as mOsm.

Table 3.—Brain Development of Immature Rats After Status Epilepticus: Protective Effect of Glucose*

	Controls	**Glucose-Injected**	**Saline-Injected**
Brain weight, mg	452 ± 24†	424 ± 18‡	404 ± 18§†
Brain RNA, μg	1172 ± 42	1141 ± 34	1093 ± 39§
Brain DNA, μg	819 ± 30	801 ± 18	753 ± 19§†
Brain protein, mg	40.8 ± 2.2†	37.6 ± 1.9‡	34.8 ± 1.8§‖
Brain cholesterol, mg	2.37 ± 0.13	2.26 ± 0.13	2.06 ± 0.14§†
RNA concentration, μg/gm	2736 ± 92	2763 ± 91	2645 ± 110
DNA concentration, μg/gm	1812 ± 64	1889 ± 42	1864 ± 44
Protein concentration, mg/gm	90.3 ± 4.5	88.7 ± 4.2	86.1 ± 4.1
Cholesterol concentration, mg/gm	5.24 ± 0.30	5.33 ± 0.29	5.10 ± 0.31
Protein-DNA ratio	49.8 ± 2.4	46.9 ± 2.1	46.2 ± 2.0
RNA-DNA ratio	1.43 ± 0.40	1.42 ± 0.40	1.45 ± 0.40
Cholesterol-DNA ratio	2.39 ± 0.20	2.82 ± 0.20	2.74 ± 0.20
Cell number, $\times 10^{-6}$	132.1 ± 4.8	129.2 ± 2.9	121.4 ± 3.1§†
Mean weight per nucleus, ng	3.31 ± 0.06	3.24 ± 0.09	3.28 ± 0.08

*Rats matched for sex, litter, and body weight (± 0.5 gm) were treated at 4 days of age and killed at 7 days of age. Treatment consisted of injection of isotonic glucose (10% of body weight) followed by two hours of flurothyl-induced seizures (glucose group), injection of isotonic sodium chloride solution followed by two hours of seizures (saline group), or simple handling (control group).

Different from controls: ‡$P < .05$; §$P < .01$

Different from glucose-injected: †$P < .05$; ‖$P < .01$

Table 4.—DNA Synthesis in Immature Rat Brains During Seizures*

Treatment	**DNA Synthesis (CPM/mg)**	**Acid-Soluble (CPM × 10^{-3}/gm brain)**	**Ratio†**
Controls	7444 ± 248‡	637 ± 55	12.33 ± 1.03‡
Seizures			
No pretreatment	4016 ± 568§	720 ± 70	5.56 ± 0.43§
Saline-treated	3970 ± 539§	718 ± 67	5.62 ± 0.64§
Glucose-treated	4796 ± 531‡§	691 ± 85	6.93 ± 0.41‡§

*Littermate 4-day-old rats were subjected to flurothyl-induced seizures every five minutes. Saline or glucose pretreatment consisted of the intraperitoneal injection (10% of body weight) of an isotonic solution 30 minutes prior to the initiation of seizures. At 60 minutes after the first exposure to flurothyl, all animals (control and experimental) received an intraperitoneal injection of [methyl-^{3}H]thymidine (5μCi/gm) and were decapitated 30 minutes later. All values represent the means of eight determinations ± 1 standard error.

†Calculated as the ratio of the mean CPM in DNA per gram of brain divided by the mean CPM × 10^{-3} in the acid-soluble fraction per gram of brain.

‡Different from the "seizure-no pretreatment" group at $P < .05$.

§Different from control at $P < .01$.

cantly reduced by glucose administration (37.1%; $P < .01$).

Influence of Glucose on Developmental Effects of Seizures

To examine the effect of status epilepticus and glucose treatment on development of the immature brain, two groups of 4-day-old rats were injected with saline or glucose and subjected to two hours of flurothyl-induced seizures. Survivors were killed three days later, and their brain weights and brain chemistries compared to those of untreated control littermates and to each other. Brain weight and brain DNA content were significantly higher in glucose-treated rats compared with saline-treated animals, but in both experimental groups, brain weights were lower than in untreated controls (Table 3). In each experimental group, brain RNA, protein, and cholesterol contents were reduced to approximately the same extent as DNA. Since diploid cells of the rat contain 6.2 pg of DNA per nucleus,[8] the mean cell deficit per brain was calculated to be 10.7 million cells in the saline group and 2.9 million cells in the glucose group. Measurements reflecting cell size (weight/nucleus, protein/DNA, RNA/DNA)[13] showed no difference among the three groups. Total brain cholesterol content was lower in saline-treated than in glucose-treated animals, but the cholesterol/DNA ratio was similar in all three groups, suggesting that lipid accumulation was reduced as part of a general reduction in the total number of cells, and not selectively.

DNA Synthesis in Brain During Status Epilepticus

The lower DNA content in the brain of immature rats subjected to repeated seizures was found previously to reflect inhibition of synthesis rather than enhanced breakdown.[14] To assess whether pretreatment with glucose would antagonize the inhibitory effect of seizures on DNA synthesis, the incorporation of tritiated thymidine into forebrain DNA was measured in untreated 4-day-old rats, and in littermates subjected to repeated flurothyl-induced seizures without pretreatment, or after pretreatment with glucose or saline. All animals given seizures accumulated the label in the cerebral acid-soluble (precursor) pool more rapidly than controls (Table 4), but incorporation of radioactivity into DNA was severely curtailed in all groups undergoing seizures. The degree of inhibition of thymidine incorporation was least marked in animals that had been pretreated with glucose.

Repeated Seizures in an Atmosphere of Oxygen

Status epilepticus in immature rats was associated with tonic apnea and cyanosis with every initial convulsion and in about 30% of subsequent convulsions. Thus, it was anticipated that, like adult animals,[15] developing rats would be protected by breathing in an atmosphere of oxygen during seizures. Four-day-old littermates were subjected to flurothyl-induced seizures for two hours in an atmosphere of room air or 100% oxygen. Of 27 animals convulsing in air, six died (22%); of 27 animals convulsing in 100% oxygen, 12 (44%) died ($P > .05$). Furthermore, the mean brain weights among the survivors, killed at 7 days of age, were similar for animals allowed to convulse in air (516 mg ± 19) or oxygen (518 mg ± 18). In other words, an atmosphere of 100% oxygen afforded no protection against the mortality or cerebral morbidity of repeated seizures. This result may be due to the fact that when substrate (glucose) is not available, increasing the oxygen supply is of little benefit. It is also possible that breathing in an oxygen atmosphere failed to prevent cerebral hypoxia.

Blood and Brain Glucose Concentrations During Seizures

In saline-treated 4-day-old rats, glucose concentrations in blood were slightly elevated before the onset of status epilepticus (perhaps reflecting the stress of injection), and remained within normal limits or slightly elevated during 50 minutes of repetitive seizures (Fig 2). In contrast, brain glucose concentrations in the saline-treated animals fell abruptly during the first series of convulsions, then more slowly over the next 20 minutes, but by 50 minutes of seizures had decreased to 30% of control. In this group of animals, the ratio of brain glucose/blood glucose level declined progressively with repeated seizures (Fig 3), suggesting that the transport of glucose from blood to brain could not keep pace with glycolytic demand.

The concentration of glucose in the intracellular fluid (ICF) of the brain of convulsing animals can be approximated from the glucose levels in blood and whole brain, assuming: (1) a brain water content of 88%[16]; (2) a brain blood volume of 3%[17] (a minimal estimate, since seizures are likely to cause vasodilation[2]); (3) an extracellular fluid (ECF) space of 20%[18-20]; and (4) a concentration of glucose in the ECF equal to 25% of the blood glucose concentration (this percentage is taken as a lower limit, since ECF glucose concentrations are probably close to those in cisternal cerebrospinal fluid, which, in turn, are usually 50% of the blood glucose level, or higher[21]). According to these assumptions, which are conservative in all instances, the concentration of glucose in the intracellular compartment of the brain is given by the expression: $[\text{Whole brain}] = 0.88\ (0.03\ [\text{Blood}] + 0.20\ [\text{ECF}] + 0.77\ [\text{ICF}])$. Substitution into this equation of the mean glucose concentrations observed in brain (0.48 mM) and blood (5.85 mM) of saline-treated rats after 50 minutes of seizures predicts an intracellular glucose concentration of about 70μM, a concentration expected to rate-limit the phosphorylation of glucose by hexokinase.[22]

In glucose-treated rats, the concentration of glucose in blood was increased about fourfold before seizures and remained well above control values for the duration of the convulsive period (Fig 2). The gradual fall in blood glucose concentration in these animals may reflect renal excretion; Clinistix tests on urine were strongly positive. Brain glucose concentrations in the glucose-injected rats were more than twice normal before the onset of convulsions, and did not change during status epilepticus.

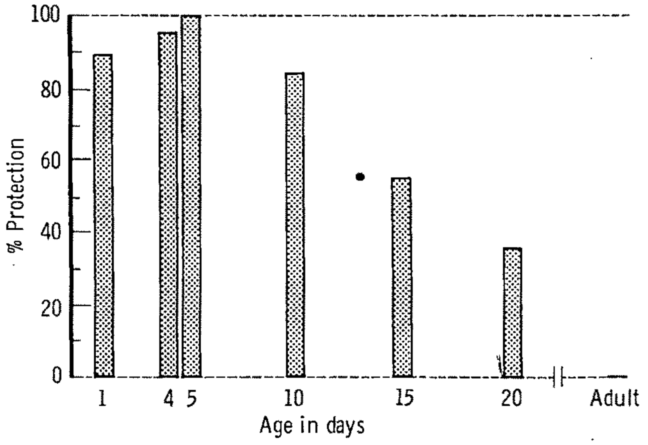


Fig 1.—Effect of glucose on mortality from repetitive seizures (see "Materials and Methods" section). Percentage protection by glucose equals (No. of saline-treated dead − No. of glucose-treated dead)/No. of saline-treated dead × 100. Total number of pairs tested in each age group was 29 (1 day of age), 103 (4 days), 13 (5 days), 16 (10 days), 12 (15 days), 13 (20 days), and 12 (adult), respectively.

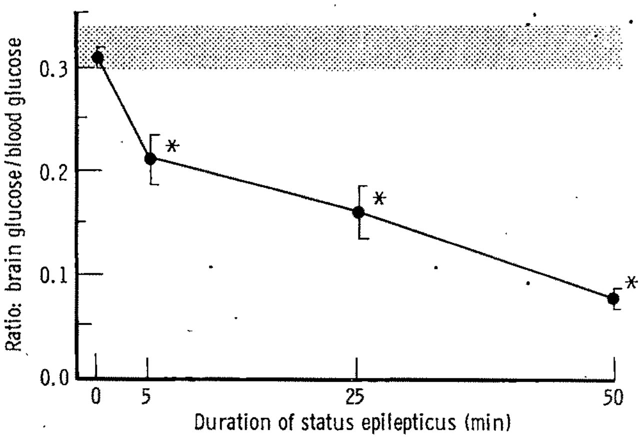
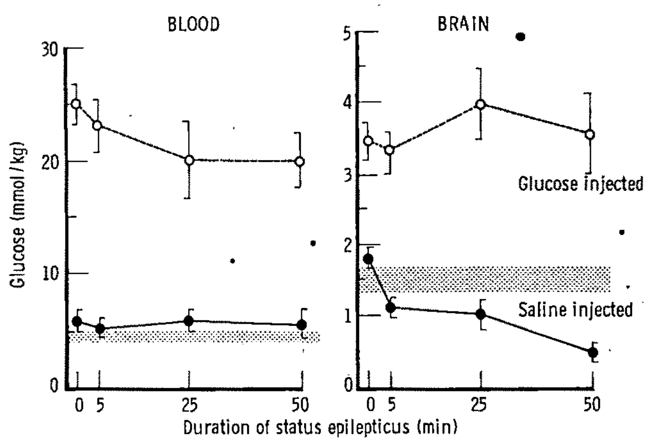


Fig 3.—Ratio of brain glucose to blood glucose concentrations in saline-treated rats. Values are calculated from data in Fig 2. Shaded area represents mean control values ± SEM. Asterisk indicates different from control at $P < .01$.

Fig 2.—Blood and brain glucose concentrations in 4-day-old rats during status epilepticus. Experimental conditions were as before except that seizures were not extended beyond 50 minutes in order to avoid data derived from moribund animals. Mortality in 4-day-old rats under these conditions was 6% in saline-treated and 0 in glucose-treated animals. Shaded area represents mean control values ($n = 5$) ± SEM. Each point represents mean of four to ten animals; vertical lines denote ± 1 standard error. In saline-injected rats, blood glucose content differed from control at 0 and 25 minutes ($P < .05$); brain glucose content differed from controls after 50 minutes ($P < .001$). All points pertaining to glucose-injected group (brain and blood) differed from control values ($P < .01$).



Lactate and ATP Content in Brain During Seizures

There was a suggestion that the accumulation of lactate in the brain, which to some extent may reflect the rate of glycolysis, was increased by glucose treatment (Fig 4). This finding implies that where more substrate was available (glucose-treated), more was consumed, giving rise to more lactate. There was no indication, however, that cerebral ATP levels were adversely affected by repeated seizures (Fig 5), nor were phosphocreatine levels in glucose-treated (3.02 ± 0.11 mmol/kg) and saline-treated (2.80 ± 0.15 mmol/kg) animals significantly different from control (3.12 ± 0.06) or from each other after 50 minutes of seizures. These data suggest that the subsequent brain damage was not simply the result of a cumulative deficit of cerebral energy reserves.

COMMENT

An impressive array of data implicates decreased glucose availability in the pathogenesis of mortality and brain damage resulting from repetitive seizures in this experimental model. Repeated seizures of sufficient intensity to cause death or, in survivors, brain damage (Table 4), were associated with a large and progres-

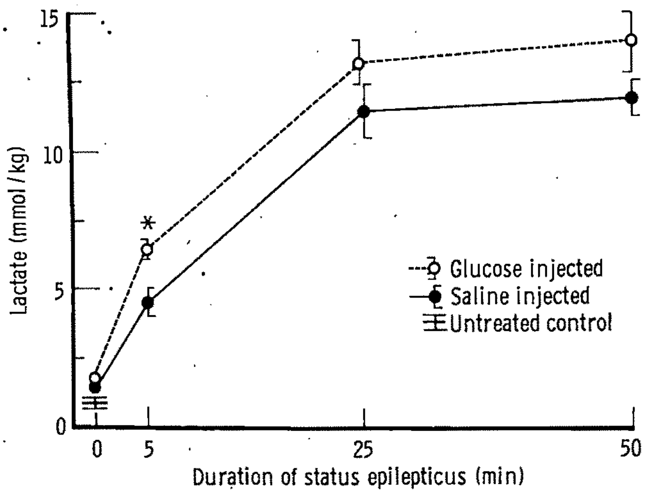


Fig 4.—Lactate concentrations in brains of 4-day-old rats during status epilepticus. Animals and experimental conditions are same as described in Fig 2. Each point represents mean of four to ten determinations ± standard error.

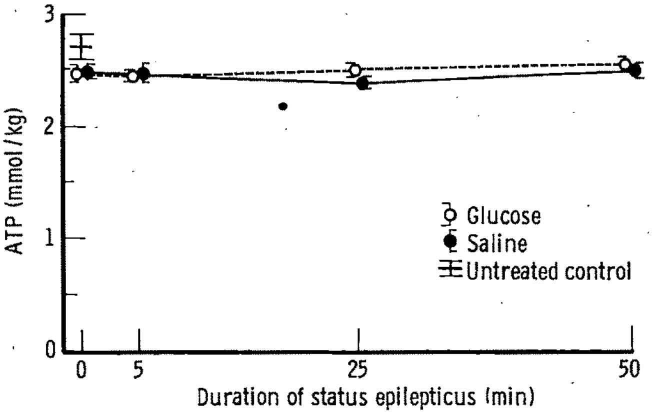


Fig 5.—Adenosine triphosphate concentrations in brains of 4-day-old rats during status epilepticus. Animals and experimental conditions are same as described in Fig 2. Each point represents mean of four to ten determinations ± standard error.

sive reduction of the glucose concentration of the brain (Fig 2). Glucose pretreatment not only prevented this depletion of brain glucose (Fig 2), but reduced mortality by 90% or more in immature animals (Fig 1), and partially prevented the adverse effects of multiple seizures on brain development (Table 3) and DNA synthesis (Table 4). These findings point to the central role of cerebral glucose depletion in the mortality and cerebral morbidity from repetitive seizures, and to the specific therapeutic advantages of glucose supplementation.

We have no direct information on whether the immediate cause of death from status epilepticus in the immature animals was cardiac, as is often the case in adults,[2] or cerebral. It seems unlikely, however, that circulation and cerebral perfusion failed in any of the experimental survivors. Moribund rats became apneic before their heart beats stopped. Depletion of cerebral ATP, which quickly follows cerebral ischemia,[23] was never observed during repeated seizures in 4-day-old animals (Fig 5). Furthermore, radioactive thymidine, injected after 60 minutes of epileptic activity, reached the brain more quickly in the convulsing animals than in controls (Table 4), suggesting that cerebral blood flow was at least adequate. The protection afforded by glucose, while substantial, was never complete; other factors, therefore, must contribute to the adverse effects of status epilepticus on the developing brain.

The observation in 4-day-old rats that cerebral ATP levels remained within normal limits even after 50 minutes of seizures was unexpected, since in adult rodents the cerebral energy reserves decline during status epilepticus.[15] It is conceivable that a decrease in ATP concentration occurred at the peak of convulsive activity,[24] but such changes were not cumulative, since rats frozen one minute after the tenth consecutive seizure episode had normal ATP concentrations in the brain (Fig 5). In this respect, the effects of seizures on the brain differ from those of anoxia, wherein the same age-dependent protection by glucose occurs but is accompanied by unequivocal decreases in ATP content and total energy reserves of the brain.[25,26] The situation in seizures seems more closely related to that observed in neonatal hypoglycemia, where an insult sufficient to impair brain development leaves cerebral ATP and phosphocreatine levels intact.[27] In the absence of evidence for energy failure, it is probable that lack of glucose during seizures impaired brain growth by depleting the organ of its main carbon source, necessary for the synthesis of macromolecules, neurotransmitters, and growth-related hormones.

The finding in 4-day-old rats that the brain/blood glucose ratio declined progressively during status epilepticus (Fig 3) suggests that glucose uptake by the brain could not keep pace with cerebral glycolysis, which in adult animals is greatly stimulated by seizures.[15] Other conditions that activate glycolysis in the developing brain, such as anoxia[23-26] or salicylate poisoning,[28] cause a similar fall in brain glucose levels at normal blood glucose levels, implying again a failure of glucose transport to match glucose utilization.

In adult and immature animals alike, glucose enters the brain from the blood via a nonenergy-requiring, carrier-mediated transport system,[29,30] the role of diffusion being negligible. The concentration of the membrane carrier has been shown to be lower in the newborn than in the adult rat brain.[31] Nevertheless, in the present experiments, glucose treatment increased both blood and brain glucose concentrations and prevented the depletion of brain glucose by repeated seizures (Fig 2). These observations probably reflect the low affinity of the transport system for glucose (K_m = 7 mM),[31] so that at physiological blood glucose concentrations (approximately 5 mM, 90 mg/100 ml), the carrier is less than one-half saturated. Increasing the blood sugar level to that obtained in the glucose-treated animals (20 mM) would be expected to double the quantity of glucose that enters the brain. In fact, during the 30 minutes between the injection of glucose and the initiation of seizures, the predicted twofold rise in brain glucose concentration was observed (Fig 2). This higher initial glucose content in the brains of glucose-treated animals may have afforded even further protection against seizures.

In animals that did not receive glucose supplements, brain glucose content fell rapidly during the first seizure, then remained relatively stable for the next 20 minutes of seizure activity, and fell again to very low levels with the next series of five seizures (Fig 2). The relative stability of the cerebral glucose concentration between the first and fifth seizures may partially reflect glycogenolysis, a slow process in the immature brain[23] (presumably owing to low phosphorylase activity[32]) and perhaps too slow to prevent some initial decrease in brain glucose level. If this speculation is correct, the subsequent fall in brain glucose level after 50 minutes of convulsive activity may represent the exhaustion of cerebral glycogen stores.

These experimental findings emphasize that during seizures the presence of a normal or even slightly elevated blood glucose concentration does not ensure adequate supplies of glucose to the brain. A similar and potentially treatable situation probably occurs in man. Assuming that the membrane transport system in the human brain has an affinity for glucose similar to that of the rat, at blood glucose concentrations ordinarily accepted as "low normal" for human infants (1.5 mM, 27 mg/100 ml), the membrane carrier should be less than 20% saturated, possibly restricting the availability of glucose to the brain. Furthermore, increasing the blood glucose concentration would readily increase the saturation of the carrier and promote the entry of glucose into the brain. In this respect, it is important to remember that the brain of the human infant is much less mature than was previously recognized,[33] and appears to be highly vulnerable to hypoglycemia.[34-37] Accordingly, when treating neonatal or infantile seizures it would seem imperative to prevent hypoglycemia and, perhaps, to maintain the blood sugar slightly elevated in order to maximize the availability of glucose to the brain.

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Mucolipidosis IV

Clinical, Ultrastructural, Histochemical, and Chemical Studies of a Case, Including a Brain Biopsy

Isabel Tellez-Nagel, MD; Isabelle Rapin, MD; Takeo Iwamoto, MD;
Anne B. Johnson, MD; William T. Norton, PhD; Harold Nitowsky, MD

• A 7-year-old Ashkenazi Jewish boy with normal early development started to regress at 8 months of age and made no further developmental progress. Corneal clouding was noted at age 10 months. Corneal and conjunctival biopsy at 14 months, cerebral biopsy at 24 months, and fibroblast cultures at 32 months showed lysosomal inclusions, suggesting the storage of lipid-like and mucopolysaccharide-like material. In the brain, dense fluorescent inclusions resembled those in ceroid-lipofuscinosis. Total ganglioside content of white matter was raised, but the pattern was normal. The level of nonlipid hexosamine in the brain was normal. The cornea and conjunctiva contained electronlucent vacuoles resembling those in the mucopolysaccharidoses. Cornea, brain, and lymphocytes contained concentric membranous lamellar structures reminiscent of those in the gangliosidoses. The clinical picture and ultrastructural findings support the impression that this case belongs to a new variant of the mucolipidoses, mucolipidosis IV.

(*Arch Neurol* 33:828-835, 1976)

Considerable progress toward a classification of sphingolipid and mucopolysaccharide lysosomal storage disorders has resulted from the demonstration of a specific catabolic enzymatic defect in many of these diseases.[1,2] The mucolipidoses,[3] which remain incompletely defined, have features of both the mucopolysaccharidoses and the lipidoses. Affected children do not have mucopolysacchariduria and appear to store lipid-like and polysaccharide-like material in their tissues. The prototype of this group is generalized G_{M1} gangliosidosis where ganglioside accumulates in the nervous system and keratan sulfate-like material in the viscera.[4] Others include mucolipidoses types I (lipomucopolysaccharidosis), II (I-cell disease), and III (pseudo-Hurler polydystrophy), fucosidosis, mannosidosis, ceramidosis (Farber lipogranulomatosis), and metachromatic leukodystrophy with multiple sulfatase deficiency.

Recently, a new variant of mucolipidosis, so-called mucolipidosis IV, was reported by Berman et al.[5] Within a year, three other cases were discovered in Israel.[6] The parents of these four children were all Ashkenazi Jews originating from southern Poland. The children were noted to have cloudy corneas soon after birth. Profound retardation became evident by age 1 year. They are described as physically attractive, without skeletal deformity, organomegaly, gross abnormality of the neurologic examination, or seizures. They did not excrete mucopolysaccharide in excessive amounts in the urine. Ultrastructural study of skin fibroblasts and conjunctiva suggested abnormal accumulation of both polysaccharide-like and lipid-like materials, which remain to be characterized. Prenatal diagnosis, based on the ultrastructural appearance of cultured amniotic cells, appears possible.[7]

We describe here an additional example of mucolipidosis IV, including chemical, histochemical, and ultrastructural information obtained from a cerebral biopsy.

REPORT OF A CASE

A 7-year-old boy has spent the last five years in a facility for the retarded. He was born at term after an uneventful pregnancy and delivery to a nonconsanguinous Ashkenazi Jewish couple aged 25 and 24 years. Their ancestors came to the United States from Warsaw, Poland, Hungary, and Austria. There is no family history of neurologic disease. The paternal grandmother and her sister developed retinitis pigmentosa in middle life, but none of their forebears or descendants are known to have had this disease. An older brother, aged 8½ years, is well. The patient was noted at birth to have a high arched palate and dysplastic pinnas. General health and somatic growth have been normal, except that the boy became microcephalic by age 4½ years. Early motor development was normal; adaptive development was slow. He smiled at 3 months. At 8 months, he did not play or respond emotionally. At 14 months, he no longer pulled to standing. No further regression has occurred, and, at 7

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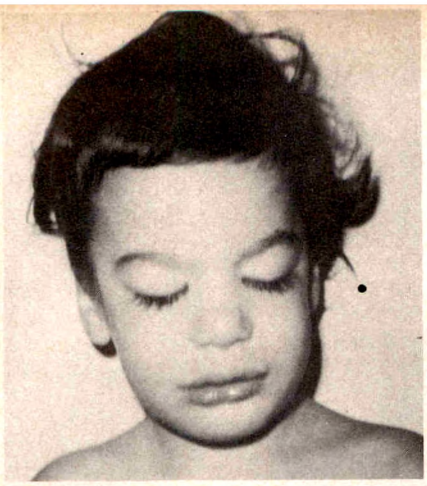

Fig 1.—Patient at 4 years of age. No skeletal or cranial abnormalities present. Facies unremarkable except for low-set ears.

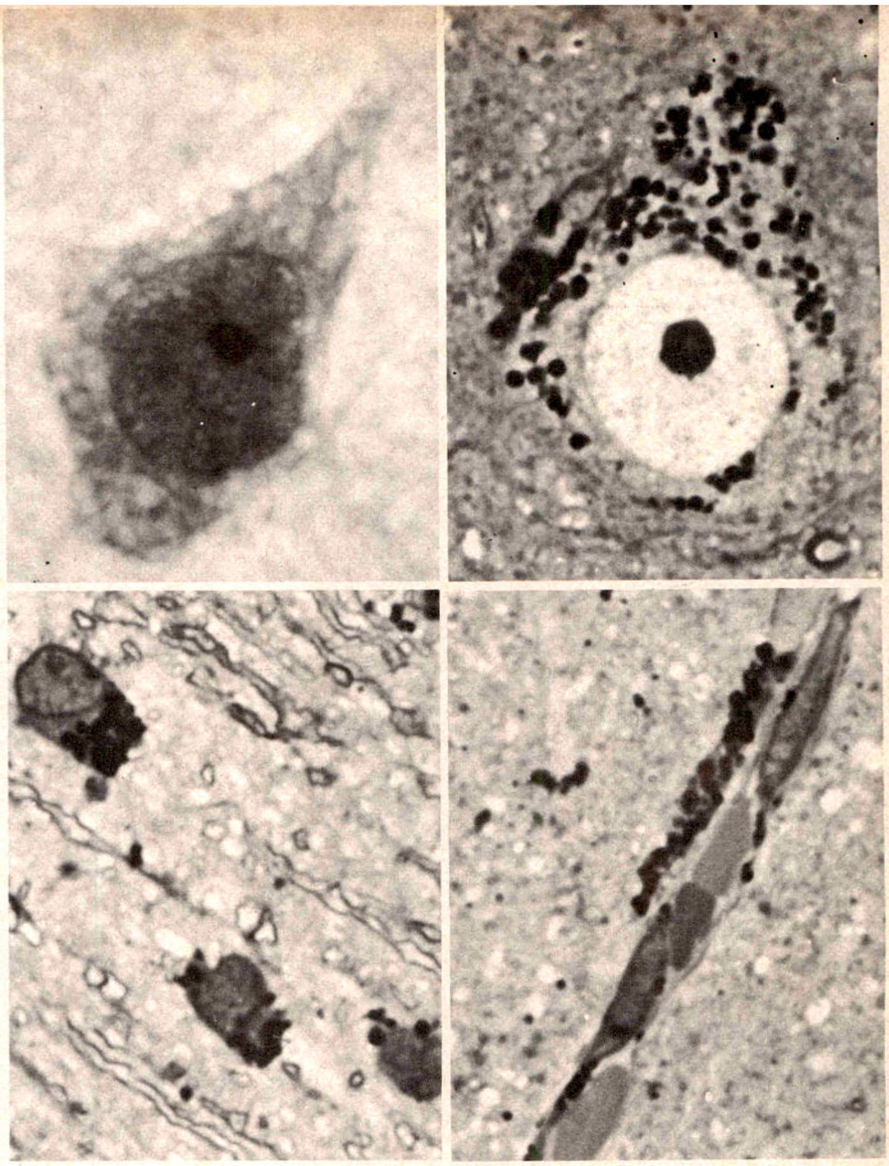

Fig 2.—Top left, Neurons of cortex contain storage bodies with very slight perikaryal swelling (hematoxylin-eosin, original magnification ×1,000). Top right, Neuron and satellite glia filled with densely stained granules (toluidine blue epoxy resin, original magnification ×400). Bottom left, White matter oligodendrocytes contain storage matter (toluidine blue epoxy resin, original magnification ×400). Bottom right, Endothelial and perithelial cells also contain storage material (toluidine blue epoxy resin, original magnification ×400).

years, he moves about sitting on his haunches. He does not feed himself, is not toilet trained, responds to no verbal commands, has developed no speech, and does not play with objects. He localizes sound, smiles and laughs to himself, but pays little attention to his environment (Fig 1). He has had no seizures.

Poor vision was suspected at 10 months, and examination showed diffuse, dense corneal clouding. This decreased substantially by 24 months, permitting funduscopic examination for the first time, but variable clouding has been present on all subsequent examinations. The lens is clear. The retina has an unusual sheen, suggesting early tapetoretinal degeneration, but there are no clumps of pigment or macular changes. The vessels appear thin; the optic disk is pale. An electroretinogram could not be obtained.

Repeated examinations have shown no skin, joint, or bony abnormality, and no organomegaly. The back is kyphotic, but there is no scoliosis or gibbus. Tone has been normal or somewhat decreased, with a tendency to scissoring when he is held upright. Tendon stretch reflexes have always been hyperactive, with clonus and upgoing toes. There is no muscular wasting. He responds to pinprick by crying. He drools excessively, but swallows without difficulty.

Normal results were obtained from the following laboratory tests at 24 months: blood cell count, urinalysis, serum electrolytes, fasting blood sugar, blood urea nitrogen, serum protein electrophoresis, karyotype in cultured leukocytes, paper chromatography of the urine for aminoacids, electromyography, nerve conduction velocities, and intravenous pyelography. Transaminase levels were mildly elevated (serum glutamic oxaloacetic transaminase, 84 and 74 units; serum glutamic pyruvic transaminase, 54 units). Electrocardiogram was normal, except for a partial right bundle branch block. Bone marrow was normal at 14 months and 27 months, without storage cells. Skeletal survey at 32 months was not suggestive of a mucopolysaccharidosis. Electroencephalogram at 14 months was mildly slow; at 23 months, it was normal, without paroxysmal features. At 24 months, a pneumoencephalogram showed mild ventricular dilation; the cerebrospinal fluid protein content was 7 mg/100 ml. Twenty-four-hour excretion of mucopolysaccharides at 1, 2, and 3 years was normal.

The following biopsy specimens were obtained without incident: right cornea and conjunctiva at 14 months, right frontal lobe at 24 months, and skin for fibroblast culture at 32 months. Informed consent for each biopsy was obtained from the parents.

MATERIALS AND METHODS

Brain Biopsy

A sample of frontal cortex with a few millimeters of subcortical white matter was obtained. Fixation and staining methods for histology, enzyme histochemistry, and electron microscopy have been detailed elsewhere.[8]

Histology, Histochemistry, and Electron Microscopy.—Paraffin sections were stained by classic neuropathological procedures. To study the properties of the storage material in brain cells, frozen sections and cryostat sections postfixed in a 10% formaldehyde solution were stained with PAS, oil red O, and Sudan black B with and without a ten-minute pretreatment with ethanol or acetone. Some fixed and unfixed cryostat sections were treated with diastase or extracted with acid-alcohol, ether, chloroform or chloroform-methanol (2:1) for 30 minutes and for 8 days at room temperature, then fixed in a 10% formaldehyde solution and stained with PAS. Metachromasia was studied in Alcian blue, crystal violet (0.1% at pH 2.8), and 0.1% aqueous toluidine blue preparations. In addition, cryostat sections were stained with 0.05% Alcian blue at pH 5.7 with both 0.1M and 0.3M $MgCl_2$ to detect mucopolysaccharides.[9] Autofluorescence was studied in deparaffinized sections fixed in a 10% formaldehyde solution. A mercury ultraviolet light source was used with filters 47 and 50. The emission spectrum was measured at a wavelength of 470 Angstroms. Acid phosphatase activity was studied in frozen sections, fixed in a 10% formaldehyde solution and glutaraldehyde, by the Gomori method and examined with the light and electron microscopes. For electron microscopy, gray and white matter were fixed in 5% glutaraldehyde in 0.067M phosphate buffer (pH 7.35) with 5% sucrose, postfixed in Dalton solution,[10] and 1-μm sections were stained with toluidine blue. Ultrathin sections from selected blocks were studied by electron microscopy.

Chemical Analyses.—A portion of the biopsy sample was dissected into gray (287.0 mg) and white matter (55.2 mg), immediately frozen in dry ice, and stored at −90 C until analyzed. Extraction of the tissue and determination of water, insoluble residue, upper phase weight, total lipid content, and individual lipid contents were carried out as previously described.[11,12] Analysis of ganglioside *N*-acetylneuraminic acid (NANA) was performed by gas-liquid chromatography.[13] Cerebrosides and sulfatides were separated on a silicagel high purity plate, using the solvent system $CHCl_3$-CH_3OH-H_2O, 70:30:4 (v/v/v). The zones were visualized by iodine vapor, scraped off, and assayed quantitatively by gas-liquid chromatography.[14] For the determination of nonlipid hexosamine, 10 mg of the lipid-free insoluble residue was hydrolyzed with 2 ml of 1N HCl in a sealed, evacuated ampule at 10 C for 15 hours. The hydrolysate was filtered, dried, and assayed for hexosamine by the Elson-Morgan reaction.[15]

Ocular Tissue

Tissue from the peripheral cornea and conjunctiva was obtained surgically by superficial keratectomy and conjunctival biopsy. Half of the tissue was processed for electron microscopy.[16] The other half was fixed in absolute alcohol, processed for histochemistry, and stained with Alcian blue, toluidine blue, and PAS.

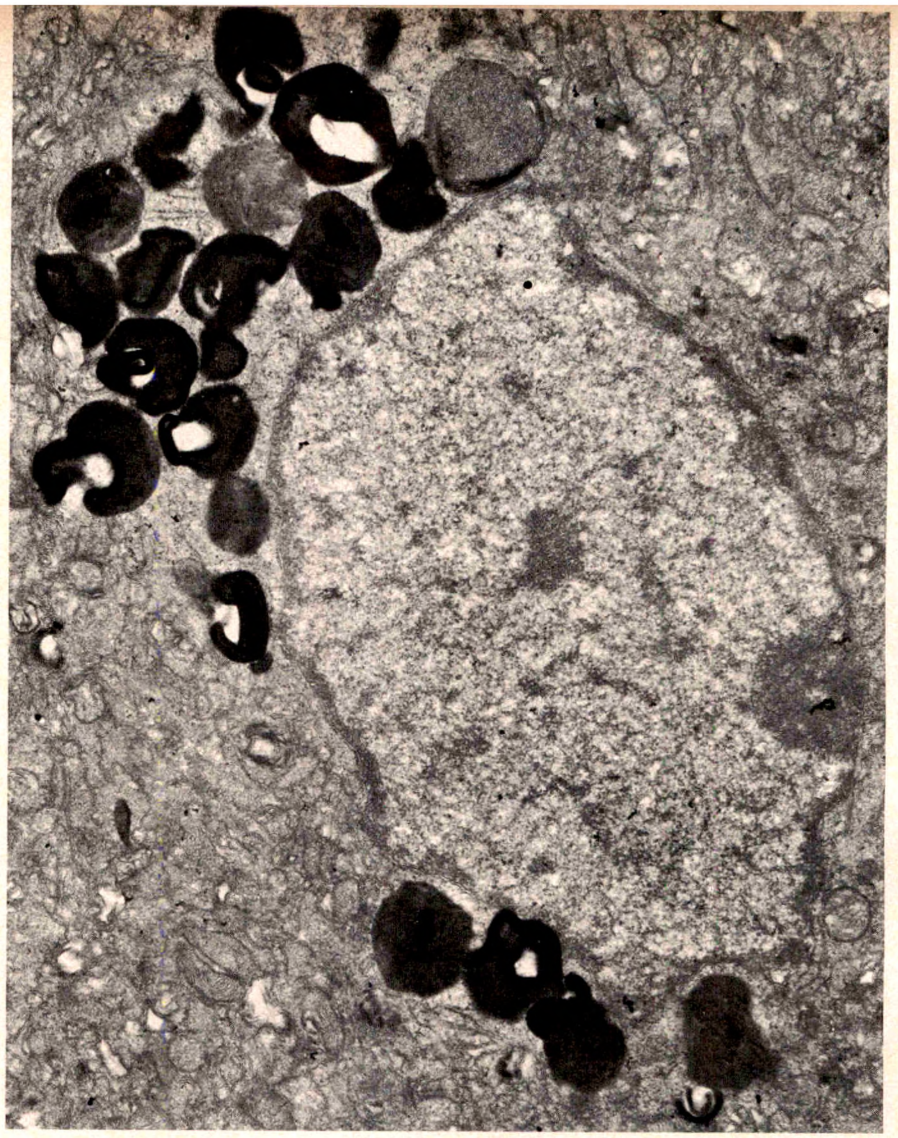

Fig 3.—Cortical neuron with perikaryon occupied by numerous compound storage bodies (original magnification ×20,250).

Cultured Skin Fibroblasts

A cell culture strain was derived from a skin biopsy specimen obtained without anesthesia, using a high-speed electric rotating biopsy punch with a core drill 3 mm in diameter.[17] The core of skin was minced into 20 or 30 fragments and cultured in McCoy 5A medium with 20% fetal calf serum at 37 C in an atmosphere of 5% CO_2 in air. After the first subculture, the cells were transferred in replicate to T flasks. After seven to eight days, the confluent monolayer of fibroblast cells was dispersed with 0.05% trypsin containing 0.2% edetic acid in calcium and magnesium-free Hank solution, and transferred to fresh medium for determination of enzyme activity. Washed cell suspensions were stored in 0.25M sucrose at −70 C for as long as three to four weeks prior to assay. Preliminary studies showed no decrease in enzyme activity with storage for this duration. Cell-free extracts were prepared by sonic vibration of thawed cell suspensions to which 0.1% octoxynol-9 (Triton X-100) was added (three parts cell to one part octoxynol-9) for one minute, using an ice water-cooled oscillator. Assays were carried out within one hour of sonication.

The amount of a given glycosidase activity at pH 4.3 in the cell sonicate was determined by a modification of the procedure of Bosmann,[18] using the following substrates: *p*-nitrophenyl-*N*-acetyl-*β*-D-glucosaminide, *p*-nitrophenyl-*α*-D-glucoside, *p*-nitrophenyl-*α*-D-galactoside, *p*-nitrophenyl-*β*-D-glucoside, *p*-nitro-

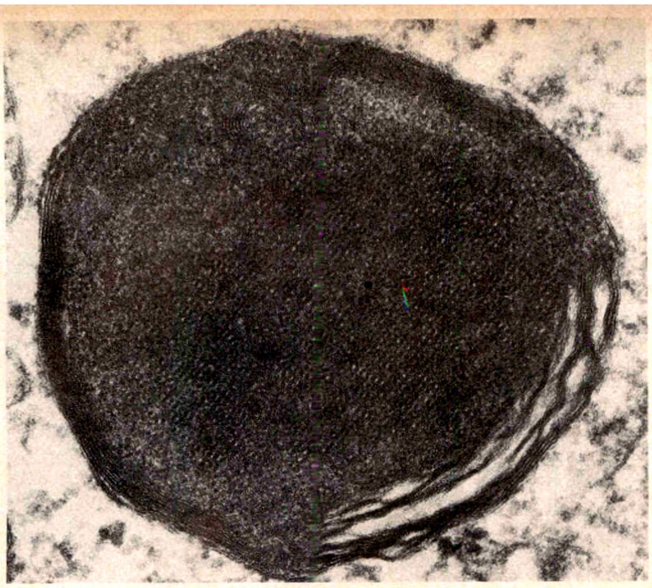

Fig 4.—Most common type of storage body (compound bodies). Compact lamellae with 50- to 60-A periodicity form the periphery and slowly blend into granular matrix that occasionally has fine crystalline pattern (original magnification × 75,500).

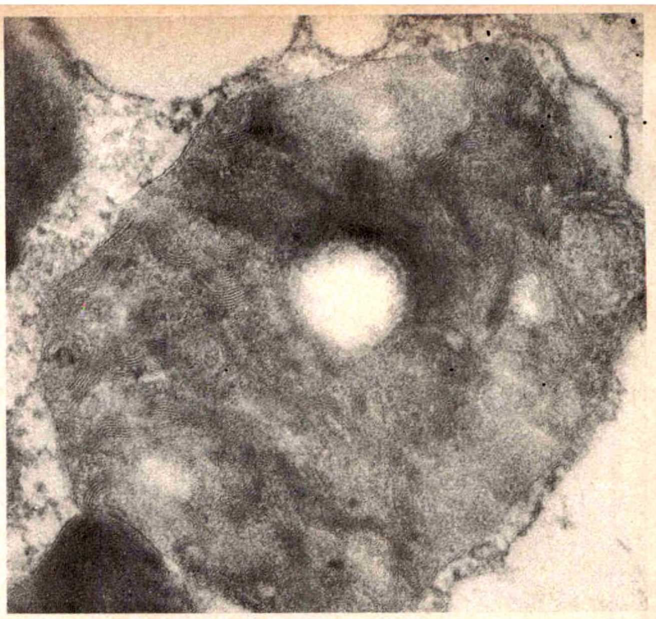

Fig 5.—Different types of inclusion bodies in oligodendrocytes formed by very densely packed lamellae, suggesting sometimes a fingerprint pattern (original magnification × 75,000).

Table 1.—Chemical Composition of Gray Matter

	Present Case	Controls*	
		Average	Range
Water, % dry weight	83.1	84.2	82.3-85.9
CHCl$_3$-CH$_3$OH insoluble residue, % dry weight	55.7	52.0	49.3-53.5
Upper phase solids, % dry weight	10.0	14.3	11.6-17.1
Total lipid content, % dry weight	34.3	31.1	30.1-32.8
Nonlipid hexosamine, ng/ng insoluble residue	9.1	11.0†	. . .
Ganglioside NANA, ng/gm wet weight	1280	812‡	744-918‡
Weight % of Total Lipid Content			
Cholesterol	23.7	22.6	21.2-23.8
Total galactolipid	4.9	3.2	2.3-5.0
Total phospholipid	72.2	69.4	64.8-75.1
Phosphatidyl choline	27.3	28.4	26.7-29.8
Ethanolamine phosphatides	19.2	21.7	18.4-26.8
Sphingomyelin	7.0	6.8	4.4-8.4
Phosphatidyl serine + phosphatidyl inositol	12.1	11.9	10.0-13.9

*Control values, with the exception of hexosamine and *N* = acetylneuraminic acid (NANA), are the averages of five normal samples, patients' ages 2.5 months, 3 years, and 8 years[43]; 5.5 years[44]; and 8 years.[12]

†From Suzuki et al.[45]

‡From Suzuki.[38]

phenyl-*β*-D-galactoside, *p*-nitrophenyl-*β*-D-fucopyranoside, and *p*-nitrophenyl-*α*-D-mannopyranoside. *p*-Nitrophenol was used as standard. Parallel substrate blanks were determined with each estimation. The proportion of heat labile *N*-acetyl-*β*-D-glucosaminidase activity was determined by measurement of residual activity of cell extracts heated in a 50 C water bath for three hours prior to enzyme assay. Total protein content was determined by a modification of the Lowry method.[19] Crystalline bovine serum albumin was used as a standard.

Electron microscopy was performed on pellets of cultured skin fibroblasts obtained by centrifuging the sample at 2,000 rpm for 10 to 15 minutes. The pellets were fixed 90 minutes in 2.5% glutaraldehyde and then 45 minutes in 1% osmium, both in Millonig buffer. Dehydration, embedment, and sectioning were standard.

Peripheral Blood Leukocytes

Leukocytes and platelets were separated from citrated peripheral blood.[20] The pellet was prepared for electron microscopy in the same manner as skin fibroblasts.

RESULTS

Brain Biopsy

Light Microscopical Observations.—The cytoarchitecture of the cortex was slightly disturbed due to spatial disorientation of the nerve cells, but there was no conspicuous loss of neurons. The majority of nerve cells were not enlarged. There were however, scattered neurons that had an enlarged perikaryon and exhibited fine, pale granularity of the cytoplasm in routine hematoxylin-eosin preparations (Fig 2, top left). There was widespread accumulation of PAS-positive granular material in all neurons. The granules stained gray with Sudan black B. The PAS staining and sudanophilia persisted after diverse extraction procedures, but the PAS reaction was somewhat diminished after a week in 60 C chloroform-methanol. The granules stained faintly pink in Cajal gold chloride preparation; they stained with Luxol fast blue (Fig 2, top right) and lightly with Heidenhain iron-hematoxylin. Similar material was present in glial cells, principally in oligodendroglia of both the gray and white matter, and in pericytes (Fig 2, bottom left and right). The material stored in neurons, glial cells, and endothelial and perithelial cells was autofluorescent.

Aqueous 0.1% toulidine blue failed to demonstrate metachromatic staining of the storage material. The Alcian blue preparation used[9] is an improved and more specific method for mucopolysaccharides, but no alcianophilia was detected. Acid phosphatase preparations showed unusually

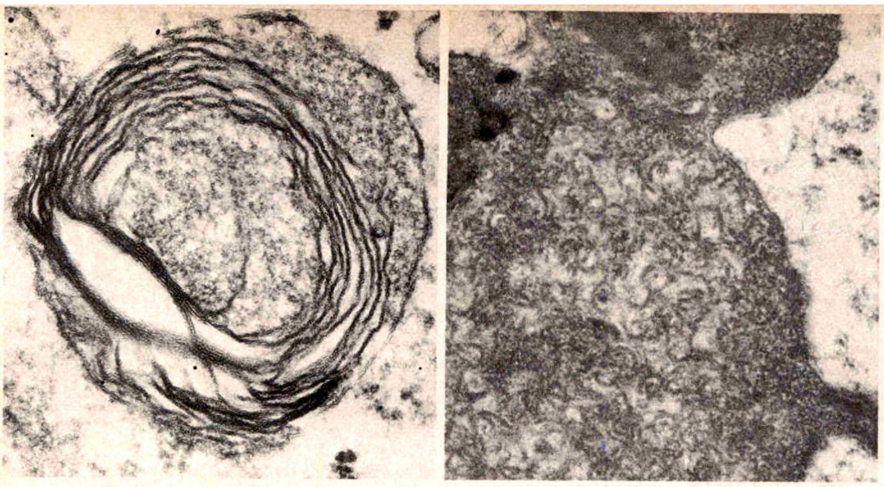

Fig 6.—Two other types of inclusions found in neuronal perikarya. Left, Membranocytoplasmic bodies. Right, Dense body with curvilinear profiles (original magnification ×50,000).

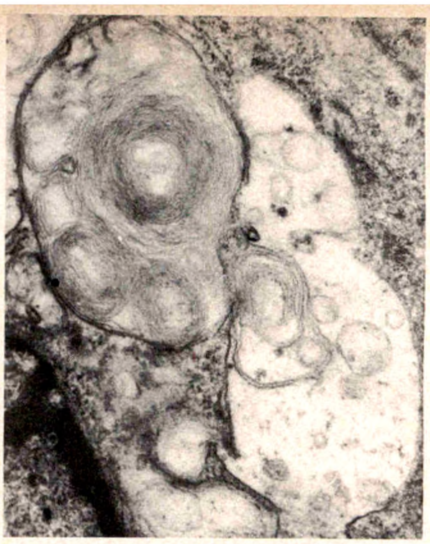

Fig 7.—Conjunctival epithelial cell with vacuoles containing both membranous lamellar bodies and fibrillogranular elements (original magnification ×25,000).

Table 2.—Chemical Composition of White Matter

	Present Case	Controls* Average	Controls* Range
Water, % dry weight	79.0	72.9	72.5-73.3
$CHCl_3$-CH_3OH insoluble residue, % dry weight	40.6	29.3	27.0-32.9
Upper phase solids, % dry weight	20.4	7.9	5.7-9.6
Total lipid content, % dry weight	39.0	54.1	52.7-56.3
Ganglioside NANA, ng/gm wet weight	887	110†	80-180†
Weight % of Total Lipid Content			
Cholesterol	26.8	26.0	24.0-27.8
Total galactolipid	15.4	26.6	25.0-29.5
Cerebroside	11.0	21.1	19.5-23.8
Sulfatide	4.4	4.6	4.0-5.5
Total phospholipid	57.8	45.1	42.5-49.4
Phosphatidyl choline	23.6	13.5	12.5-14.6
Ethanolamine phosphatides	17.0	15.5	14.1-17.1
Sphingomyelin	9.4	7.9	7.5-8.5
Phosphatidyl serine + Phosphatidyl inositol	15.9	8.9	7.9-10.2

*Control values, with the exception of *N*-acetylneuraminic acid (NANA), are averages of four normal samples, patient ages 3 years and 8 years[43]; 5.5 years[44]; and 8 years.[12]

†From Suzuki.[38] It should be noted that Yu and Ledeen[13] find much higher values for normal white matter (267 μg of NANA per gram of wet weight).

large, strongly positive granules in the neuronal cytoplasm, and sometimes these extended into the proximal axon, as found in other storage disorders. Acid phosphatase reaction product also occurred in cortical glia and in capillary endothelial cells. A few perivascular macrophages had large, globular collections of oil-red-O- and Sudan-black-B-positive, acetone-extractable lipid. There was widening of the Virchow-Robin spaces. The staining properties of myelin were normal in Heidenhain and Luxol fast blue preparations. The axis cylinders appeared normal in Bodian preparations.

Ultrastructural Observations.—Numerous dense storage bodies were present in neurons (Fig 3), oligodendrocytes, and in endothelial and perithelial cells. They were usually round or oval, limited by an outer membrane, and varied in size from 0.5 μ to 2.0 μ (Fig. 4 and 5). Two main types of inclusions were recognized: (1) A previously undescribed compound body (CB) with a lamellar and a granular component blending into one another (Fig 4). They were membrane-bound and contained acid phosphatase activity only in the granular matrix. Stacks of 10 to 20 osmiophilic membranes, with a center to center periodicity of 50 to 55 A, were situated at the periphery or at one end of the body. Sometimes the granular core had an internal substructure resembling a crystalline lattice (Fig 4). (2) The second most common storage body was very dense, strongly osmiophilic, and had a fine lamellar structure that was difficult to define at magnifications below ×100,000. This second type was most prevalent in oligodendrocytes (Fig 5).

In addition to these main types of inclusions, there were bodies resembling the membranocytoplasmic bodies (MCBs) described in gangliosidosis[21] and curvilinear bodies described in ceroid lipofuscinosis.[22] Transitional forms to membranous bodies and to curvilinear bodies were occasionally seen (Fig 6). Lipofuscin was present in small amounts in astrocytes.

Neuronal mitochondria appeared normal. The endoplasmic reticulum was slightly dilated. The perikaryon was occupied to a large extent by the abnormal storage bodies. No transition between these bodies and other cell organelles was observed. Occasional dilated axons with dense bodies and multilamellar cytosomes were seen in the neuropil. The synapses were normal.

Chemical Analyses.—The results of the analytical study are presented in Tables 1 and 2 together with control values. The composition of the gray matter was within normal limits, with the exception of the gangliosides. It should be noted that the level of nonlipid hexosamine was not elevated.

Table 3.—Activity of Acid Hydrolases in Skin Fibroblasts

Enzyme Activity*	Present Case	Controls (N = 4)†
N-acetyl-β-D-glucosaminidase (% thermolabile‡)	9,933 (73)	4.676-10,188 (52-73)
α-D-glucosidase	80	64-101
β-D-glucosidase	100	50-192
α-D-galactosidase	47	52-92
β-D-galactosidase	535	398-795
α-D-mannosidase	47	64-77
α-D-fucosidase	67	36-73

*Activity expressed as millimicromoles of substrate hydrolized per hour per milligram of protein.
†Maximum range of activity.
‡Residual activity after thermal inactivation of 50 C for three hours.

The composition of the white matter was abnormal, having more water and a lower lipid-protein ratio than the control values. The white matter lipids had a normal amount of cholesterol, but were lower in galactolipid and higher in phospholipid than the control samples. It is probable that some of these white matter differences can be attributed to the earlier maturational stage of the patient compared to even the youngest control value.

The major abnormality in both gray and white matter was the ganglioside content, which was elevated approximately 50% in gray matter and at least threefold in white matter. Qualitative thin-layer chromatography of these gangliosides showed a relatively normal ganglioside distribution in both gray and white matter, although both samples had somewhat more G_{M_1} and G_{M_2} (the monosialogangliosides) than controls. However, in neither sample was there a specific notable elevation in any individual ganglioside.

Ocular Tissue

Ultrastructurally, corneal epithelial cells had numerous vacuoles in the cytoplasm, often displacing the nucleus toward the base of the cell. The vacuoles contained loosely arranged fibrillogranular elements and cellular debris. A few epithelial cells in the middle layer had membranous lamellar inclusions. Keratocytes (fibroblasts) in the superficial corneal stroma had dilated rough-surfaced endoplasmic reticulum or smooth-surfaced vacuoles or both. The content of these vacuoles was finely granular, but occasional lamellar structures could also be seen. Some conjunctival epithelial cells had large cytoplasmic vacuoles containing both fibrillogranular and membranous lamellar inclusions in myelin-like figures (Fig 7). Endothelial cells of small blood vessels and of lymphatics in the subjunctival connective tissue had membrane-bound inclusions filled with membranous lamellar bodies or with granular or vesicular components. The lamellae were usually at the periphery of the vacuoles, with the granular and vesicular components in the center. Lymphocytes, plasma cells, and macrophages contained membranous lamellar inclusions.

The vacuolated epithelial cells of the cornea and conjunctiva, as well as the keratocytes and surrounding stroma, showed positive staining with Alcian blue and PAS and were metachromatic with toluidine blue. Endothelial cells of conjunctival blood vessels stained positively with PAS.

Fibroblast Cultures

Fibroblasts from the patient were large, and all contained abnormal storage granules or vacuoles. The enzyme activities of the patient's fibroblasts were all within the normal range (Table 3).

Ultrastructurally, the storage bodies consisted of orderly arranged lamellae and a granular component usually present within large membrane-bound cytoplasmic vacuoles (Fig 8 and 9). Most vacuoles appeared empty, but a few contained small amounts of moderately electron-dense material. The lamellar-granular bodies resembled the CBs found in the brain. Their presence within the vacuoles in apparently different stages of morphological development suggests that they formed within the vacuoles, eventually enlarging to occupy and replace them. Large aggregates of glycogen granules were present in the cytoplasm of many cells.

Skin fibroblasts grown in a culture from the healthy, 27-year-old mother of the patient showed identical ultrastructural storage material, but fewer cells were involved and fewer granules per cell were present. A conjunctival biopsy of the mother showed no evidence of storage by electron microscopical and histochemical criteria.

Blood Cells

Blood smears showed no abnormalities by light microscopy. Electron microscopy of the buffy coat showed dense lamellar inclusion bodies in the lymphocytes. The storage was limited to only a few storage bodies per section. No vacuolated cells were found.

COMMENT

The findings in this child are similar to those of the four patients described by Berman et al[5] and Merin et al.[6] In this disorder, lysosomal storage suggesting a catabolic block has been found in many tissues, including keratocytes, epithelial conjunctival cells, hepatocytes,[5] Kupffer cells,[5] and skin fibroblasts. Our patient, in addition, showed storage in neurons, glia, perivascular cells of the brain, circulating lymphocytes, and cultured fibroblasts.

In the brain of our patient, inclusions (CBs) were mainly electron dense, fluorescent bodies. Transition forms between these bodies and concentric lamellar inclusions (MCBs) or bodies with curvilinear profiles were infrequent. The MCBs and the CBs had a periodicity of 50 to 60 A, which coincides with the ultrastructure of MCBs in other gangliosidoses.[21-23] The transitional forms with curvilinear profiles resembled the bodies found in several variants of the ceroid lipofuscinoses.[24-25] No clear-cut lipofuscin granules were found in the neurons of our patient, although most bodies had autofluorescent properties and were resistant to extraction with chloroform-methanol, in keeping with the properties of the so-called lipopigments (ceroid and lipofuscin).[26]

The inclusions in skin fibroblasts in

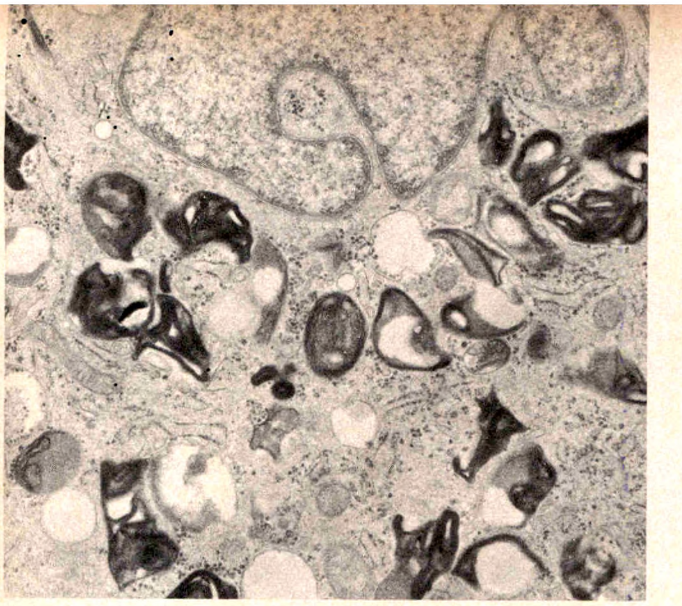

Fig 8.—Cultured skin fibroblast. Cytoplasm filled by dense storage bodies and clear membrane-bound vacuoles (original magnification ×10,000).

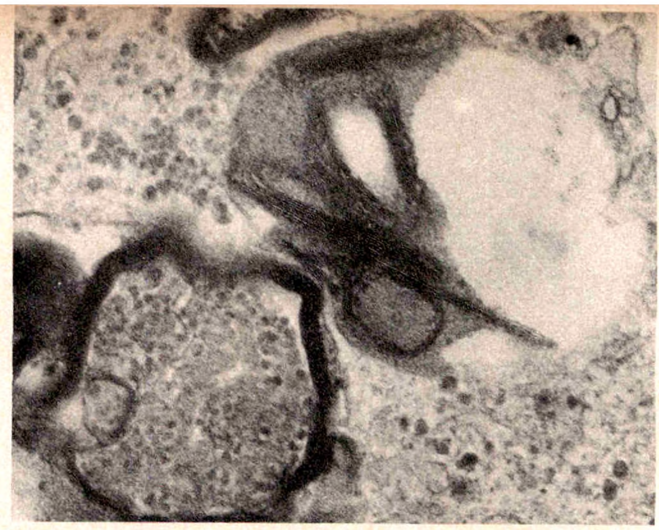

Fig 9.—Detail of storage material in skin fibroblasts. Vacuoles often contain lamellar inclusions. Glycogen-like granules seen free in cytoplasm and within inclusion bodies (original magnification ×66,000).

our patient were both clear vacuoles and dense bodies with straight, parallel lamellae. Electrolucent vacuoles and accumulations of glycogen in the cytoplasm, such as those seen in our patient, have been observed in hepatocytes[27] and in fibroblast cultures in Hurler syndrome,[28] in chondroitin-4 sulfate mucopolysaccharidosis and in Sanfilippo disease.[29] Berman and coworkers[5] found mostly concentric lamellar inclusions in their patient's mucolipidosis IV. The ultrastructural abnormality of fibroblasts in our patient suggests storage of lipid and possibly also of mucopolysaccharide.[29] To our knowledge, electron microscopical evidence of storage in cultured fibroblasts of a clinically unaffected heterozygote parent has not been reported previously. This aspect is now under further investigation because of its possible implications in the differential diagnosis in amniotic cells.

The corneal epithelial cells and keratocytes were vacuolated and contained some fibrillogranular structures. Both cells showed alcianophilia, metachromasia with toluidine blue, and PAS positivity. Similar pathologic morphology and histochemical behavior of the cornea were reported in Hurler disease[30] and in G_{M_1} gangliosidosis.[31] Endothelial cells of blood vessels and lymphatics of the conjunctiva, as well as lymphocytes, plasma cells, and macrophages, contained abundant membranous lamellar bodies. These inclusions were PAS-positive, although they did not stain with Alcian blue or exhibit metachromasia. Similar inclusions have been found in retinal ganglion cells in G_{M_1} gangliosidosis and thought to be ganglioside.[31] Conjunctival epithelial cells had vacuoles, some with fibrillogranular and others with lamellar bodies, suggesting the storage of both mucopolysaccharide and glycolipid substances. Similar conjunctival abnormality has been found in mucolipidosis II (I-cell disease),[32] mucolipidosis III (pseudo-Hurler polydystrophy),[33] and mucolipidosis IV.[6]

There was no evidence in our patient and in the child described by Berman et al[5] for either increased or decreased activity of any of the hydrolases measured. These findings clearly separate mucolipidosis IV from the mucolipidoses where specific hydrolase deficiencies have been found (G_{M_1} gangliosidosis, mannosidosis, fucosidosis, ceramidosis, and metachromatic leukodystrophy variant). In mucolipidosis I (which may not be a single entity), β-galactosidase activity in liver has been decreased in some patients,[34] while in others with many clinical similarities, it was normal[35] or increased.[36] It is uncertain whether β-galactosidase plays a primary role in this disorder. In mucolipidosis II, multiple hydrolases have increased activity in the extracellular spaces and decreased activity intracellularly.[37] Similar decreases of intracellular and increases of extracellular acid hydrolases in mucolipidosis type III have been described, even although these mucolipidoses are quite distinct phenotypically. The primary deficit in both remains uncertain.

The chemical finding of elevated levels of gangliosides in white matter of the brain biopsy specimen is consistent with the diagnosis of mucolipidosis, but is not specific. Similar elevations have been found in many other neurological diseases of widely varying causes.[12,38-41] It is probably that the fluorescent lipopigment stored in the brain was not detected by any of the analyses performed due to its insolubility. It is interesting that the nonlipid hexosamine content of the gray matter was normal, indicating that there cannot be significant storage of hexosamine-containing mucopolysaccharides in this tissue. The relationship between increase in the amount of ganglioside and the appearance of lipopigment is not understood, but has been noted in other diseases, for instance in an adult (chronic) variant of G_{M_2} gangliosidosis.[42] Chemical analysis of other tissues for sphingolipids and for mucopolysaccharides has yet to be carried out in this disorder. Until more chemical progress is made, it is premature to speculate on an enzymatic defect to account for storage of several complex saccharide and lipid-containing compounds.

In all five children, corneal clouding was the first evidence for a storage disease and led to further investigation. The diagnosis is most easily confirmed by ultrastructural examination of the conjunctiva. Skin fibroblasts are another readily available tissue that may be used as a model to study the basic disease process. The encouraging report of Kohn et al,[7] indicates that it is possible to detect an affected fetus by observing abnormal inclusions in cultured amniotic cells. Prenatal diagnosis and genetic counseling may be possible without having to await clarification of the fundamental biochemical process that underlies the disease. On the other hand, if the finding of a few inclusions in skin fibroblasts of our patient's mother is confirmed, it is possible that heterozygote fetuses as well as homozygous ones may show amniotic inclusions. Further experience is needed to decide this point.

Results of ophthalmologic evaluations were made available by Drs S. Trokel, MD, P. Henkind, MD, and B. Beckerman, MD, and of prior neurologic investigations by A. Chutorian, MD. J.F. Schneider, MD, provided the opportunity for follow-up examinations. The corneal biopsy was carried out by S. Trokel, MD, and the brain biopsy by K. Shulman, MD, B.S. Danes, PhD, measured the mucopolysaccharide content of the urine. M. Santorineou, MD, examined the bone marrow and blood smears, and H. Goldman, MD, examined the radiographs. R. Yu, PhD, performed the analysis of ganglioside *N*-acetylneuraminic acid. Lawrence Gonzalez and Loyda Menez provided technical assistance. Carol Tiffany carried out the analytical work on the brain biopsy samples. R.D. Terry, MD, reviewed the manuscript. E.R. Berman, MD, and G. Kohn, PhD, provided information about the Israeli cases and discussion of our case.

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Axonal Degeneration in Beriberi Neuropathy

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• Ultrastructural and teased-fiber studies were carried out on the sural nerves of nine patients with beriberi neuropathy. Axonal degeneration was the most prominent feature, and large myelinated fibers were more affected than unmyelinated ones. An unusual change with accumulation of flattened sacs or tubuli was recognized in the axoplasm of myelinated fibers of untreated patients. Active regeneration was extensive in patients receiving vitamin B_1. Segmental demyelination, remyelination, and early onion bulbs were scarce in patients with a long and relapsing course before treatment.

(*Arch Neurol* 33:836-841, 1976)

Beriberi neuropathy is endemic among people who use milled rice as a major food.[1] In Japan the disorder was rare until several years ago, mainly because vitamin B_1 was customarily added to milled rice. In recent years, however, "instant foods" low in vitamin B_1 content have become popular, leading to beriberi neuropathy among young men who take milled rice and "instant foods" without supplementary vitamin B_1 while performing heavy physical work. This report describes the morphologic characteristics of sural nerves in beriberi neuropathy. As in experimental thiamine deficiency,[2] axonal degeneration was the distinctive feature.

SUBJECTS AND METHODS

We studied nine cases of typical beriberi neuropathy (Table). All patients had taken milled rice without addition of vitamin B_1 as the main constituent of a low-fat diet. Most were fond of "instant" noodles and disliked meat or fish. Their meals were therefore rich in carbohydrate and poor in vitamin B_1. The younger patients belonged to athletic clubs; the adults were physical laborers.

Onset of the disorder was acute or subacute. Some had a relapsing course for 2 to 12 months before vitamin B_1 administration. In the acute phase and in every recurrence, they showed severe leg edema, weakness, sensory loss in the legs and sometimes the arms, loss of patellar and Achilles reflexes, apical heart murmurs, accentuated second pulmonary sounds, and cardiac enlargement. The neuropathy was predominantly motor, especially affecting distal muscles. Most of the patients could not stand or walk when symptoms were most severe. Sphincters were not affected. Cerebrospinal fluid was normal in all cases. Motor conduction velocities in posterior tibial nerves during early phases of vitamin B_1 treatment were reduced to 43, 38, 39, and 43 m/second in patients 5, 7, 8, and 9, respectively.

Serum thiamine levels were 2.5 γ/dl and 1.2 γ/dl (normal 3 to 6 γ/dl) in patients 2 and 3, respectively. Serial measurement of vitamin B_1 for four days in patient 1 gave values of 4.5 to 5.3 γ/dl in total blood thiamine (normal, 7 to 13 γ/dl); 20 to 59 γ in urinary excretion of thiamine per day (normal, 200 to 800 γ); 27 to 32 mg/dl in blood lactic acid level (normal, 9 to 16 mg/dl), and 0.3 to 0.6 mg/dl in blood pyruvic acid level (normal, 0.3 to 0.6 mg/dl). Oral administration of vitamin B_1 resulted in no increase in urinary excretion of thiamine, namely 50 γ/day in this case. The findings of low blood thiamine levels, low thiamine excretion in urine, no increase in urinary excretion by oral administration of 5 mg of vitamin B_1, and high blood levels of lactic acids were completely in accord with thiamine deficiency. Thiamine was measured by the thichrome method,[3] and lactic acid and pyruvic acid by the enzymatic method.[4] Following oral administration of vitamin B_1 (10 mg/day), edema, cardiac enlargement, and neuropathy began to ameliorate in a few weeks.

Sural nerve biopsy was performed during untreated acute stages on patients 1 and 2, and during a recurrence in patient 3 after six months of interruption of vitamin B_1 from the first treatment (Table). The other patients underwent biopsy during recovery phases after vitamin B_1 therapy. Patient 8 had been untreated for 17 months and was still not

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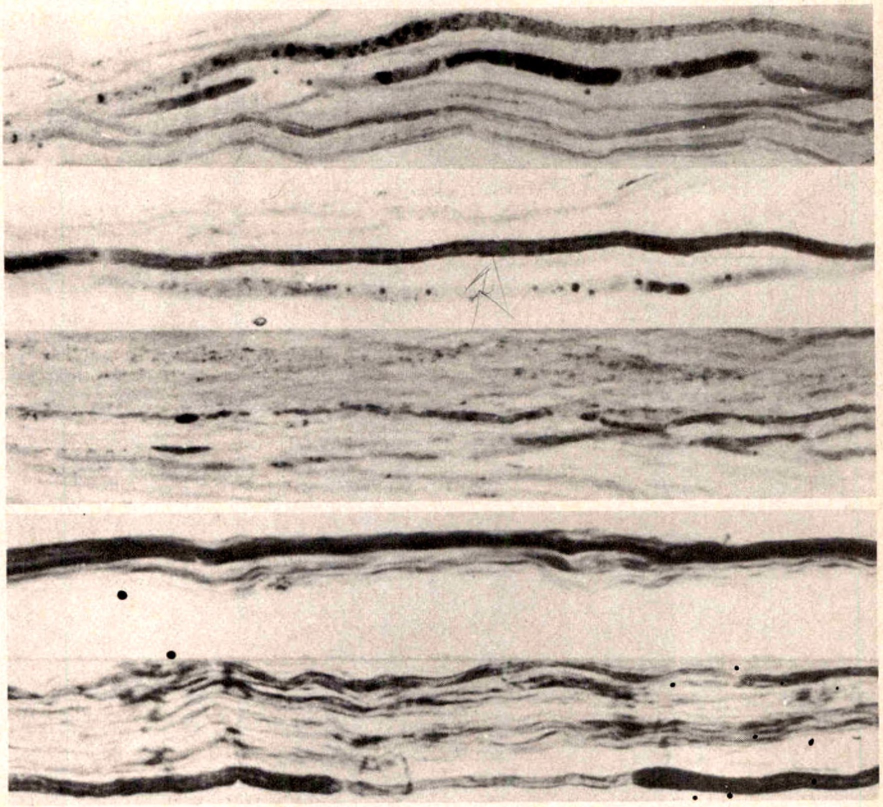
Data on Nine Patients Studied

Patient/Age, yr/Sex	Onset	Interval, Days: Onset to Therapy	Interval, Days: Therapy to Biopsy	Cardiac Enlargement	Walking	Sensory Disturbance
1/15/M	Acute	. . .	Before therapy	Yes	Difficult	Globe and stocking
2/17/M	Acute	. . .	Before therapy	Yes	Unable	Stocking
3/35/M	Acute	28	310*	Yes	Unable	Stocking
4/43/M	Acute	6	16	Yes	Difficult	Stocking
5/17/M	Subacute	41	34	Yes	Unable	Stocking
6/44/M	Acute	65	78	Yes	Unable	Stocking
7/60/M	Subacute	304	90	Yes	Unable	Stocking
8/20/M	Subacute	520	91	Yes	Unable	Globe and stocking
9/22/M	Subacute	320	30	No	Difficult	Stocking

*Vitamin B_1 therapy was interrupted at the time of biopsy.

Fig 1.—Teased fibers showing linear rows of myelin ovoids and a segmental demyelination (lowermost fiber). Top, Patient 4; bottom, patient 9.



able to walk at the time of biopsy, 13 weeks after treatment. Patients 8 and 9 showed long relapsing courses before treatment.

Biopsy specimens were fixed in 3% glutaraldehyde solution, postfixed in phosphate-buffered 1% osmium tetroxide, dehydrated through acetone series, and embedded in Epon 812. Sections were made in an ultramicrotome and stained on the grid with uranyl acetate and lead citrate.

Fiber diameter frequency histograms were made on 347 and 269 unmyelinated fibers in patients 4 and 8, respectively. Diameter of unmyelinated fibers was measured on electron-microscopic photographs with a magnification of 8,000. Profiles that could not be differentiated from Schwann cell processes were discounted.

Nerve teasing was made on the specimens of 5 mm length in all cases after fixation in 1% osmium tetroxide and maceration for two days in glycerin solution.[5] Internodal length and fiber diameter were measured with a micrometer in patient 6.

RESULTS

Light Microscopy

There was a loss of myelinated fibers with increase in amount of collagen fibers. In Epon sections stained with methylene blue, scattered fragmented myelin and myelin ovoid formations were seen. The severity of these changes corresponded to the degree of sensory loss in the leg in every case.

Teased Fibers

Linear rows of myelin ovoids were abundant in all cases (Fig 1, top). Bead-like transformed myelin sheaths were occasionally present. Among many fibers examined, a single segmental demyelination was seen only in patient 9, with a relapsing course (Fig 1, bottom). In patient 4, the relationship between internodal length and fiber diameter indicated myelinated fibers with disproportionately short internodes, suggesting axonal degeneration and regeneration (Fig 2).[5,6]

Electron Microscopy

Axonal Changes.—In patients 1, 2, and 3, sural nerve biopsy specimens taken at the onset of disease presented some unusual changes in axis cylinders: many flattened vesicular profiles of various sizes were observed, some showing a tubular structure in oblique sections. They accumulated irregularly in the axoplasm and resembled clumped neurotubules (Fig 3). Sometimes, there were numerous smooth vesicles of varying size, some with electron-dense cores, often in clusters, comingled with neurotubules to form islands separated by bands of neurofilaments (Fig 4). Sometimes, the tubular structures had the same orientation as neurofilaments. Some of the sacs showed networks encircling the neurotubuli with increased density (Fig 5). These accumulations of sacs were not found in the other patients treated with vitamin B_1 and may be an early change of beriberi

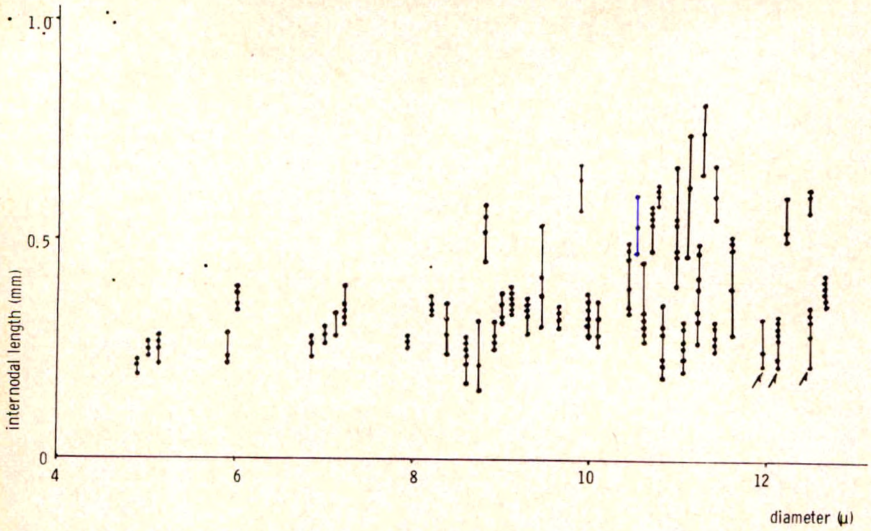
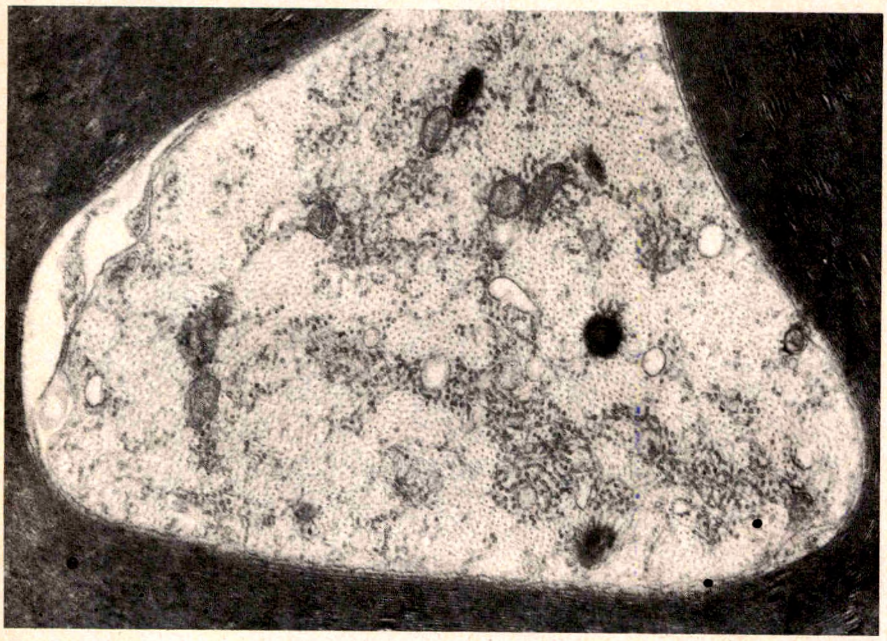


Fig 2.—Relationship between internodal length and fiber diameter in patient 6. Arrows are regenerated fibers.

Fig 3.—Sural nerve in patient 2 showing increase and clumping of tubular structure in axon (original magnification, ×15,000).



neuropathy. There were also cored vesicles and those with double membranes, probably derived from vacuolated mitochondria. Another unusual feature of degeneration was seen occasionally in myelinated fibers in patients 1, 2, and 3: axons and Schwann cells were packed with a large number of mitochondria (some degenerated), vesicles, small myelin figures, and multimembranous bodies (Fig 6). Some myelinated fibers contained floccular and electron-dense materials (Fig 7, top left), or glycogen granules (Fig 7, top right).

In addition, there were nonspecific manifestations of axonal degeneration in all cases, including disorderly arrangement or rarefaction of neurofilaments; axoplasm containing accumulation of degenerated mitochondria, vesicles, and small myelin figures; myelinated fibers in which axons were replaced by homogenous dense material; and Schwann cell cytoplasm with collapsed myelin but no axon. The lamellar structure of myelin was often preserved even in fibers with degenerated axons, indicating that axonal degeneration was the primary change. Large myelin ovoids devoid of axons were often found in Schwann cells, and macrophages contained membrane-limited structure and lamellar bodies.

Changes in the Schwann Cell and Myelin Sheath.—In general, changes of the Schwann cell and myelin sheath were less than those of axons, and appeared secondary to axonal degeneration. There were only rare myelinated axons that were atrophic, and often with an increased number of dense bodies and with endoplasmic reticulum (Fig 7, bottom left). These axons were sometimes enveloped by irregular Schwann cell processes and redundant basement membranes, which might represent demyelination secondary to axonal degeneration, as suggested by Dyck et al.[7]

Changes in Unmyelinated Fibers.—Active degeneration of unmyelinated axons was occasionally found. Increased numbers of vesicular or tubular profiles, mitochondria, and dense bodies were noticed in both axoplasm and Schwann cell cytoplasm in untreated patients. Nonspecific degeneration of the axis cylinder, fragmentation, and rarefaction of neurofilaments was seen occasionally in all patients, but these changes were slight compared to those of large myelinated fibers.

Regeneration and Remyelination.—There were a number of clusters of Schwann cell processes (Büngner bands) in all biopsy specimens. The clusters in untreated patients (No. 1 and 2) contained no definite profiles of regenerated axons, whereas those in the treated patients had many axons, some not yet individually enveloped by Schwann cell cytoplasm. There were also clusters of Schwann cells and axons, one or more of which were myelinated. The findings indicated regeneration from axonal or Wallerian degeneration. In rare instances, isolated and disproportionately thin myelinated axons were enveloped by redundant basement membranes and sometimes by Schwann cell whorls (Fig 7, bottom

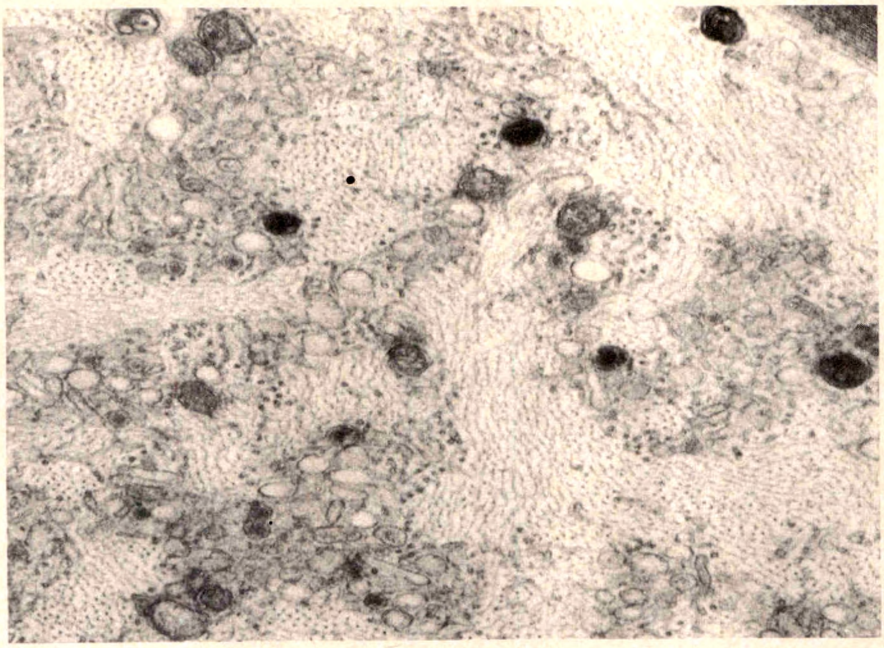
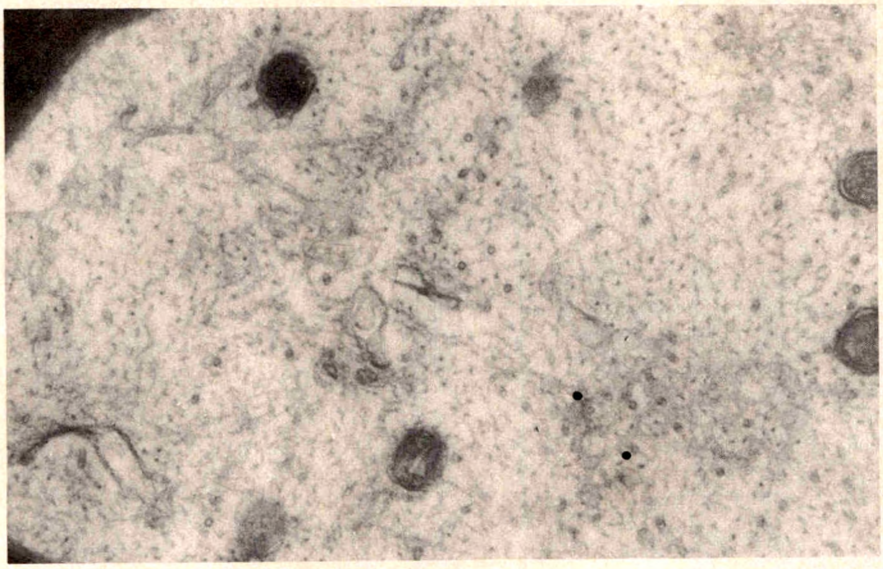


Fig 4.—Sural nerve in patient 1 showing accumulations of sacs with various size, tubular profiles, cored vesicles, and degenerated mitochondria (original magnification, ×15,000).

Fig 5.—Sural nerve in patient 1. Sacs show branching and networks (original magnification, ×28,000).



right); these signs of remyelination were recognized in patients 8 and 9, who had long and relapsing courses of 520 and 320 days, respectively, before therapy (Table). The intervals between treatment and biopsy for patients 8 and 9 were 91 and 30 days, respectively. A few myelinated fibers with slight whorl formation of Schwann cell processes were also observed in these patients. Some unmyelinated axons, swollen and packed with lamellar bodies, osmiophilic droplets, and vesicles, were seen and thought to be the tip of regenerated axons.[8,9] Small clusters suggestive of regeneration of unmyelinated fibers were only rarely seen.

Generally, regenerating features were prominent in patients receiving vitamin B_1, corresponding to the marked improvement of clinical symptoms. The diameter-frequency histograms of unmyelinated fibers from patients 4 and 8 had a bimodal distribution suggesting an increase of newly formed small unmyelinated fibers (0.2 to 0.4 μ in diameter) (Fig 8), which seem to result from regeneration.[10]

COMMENT

The disorder in these patients was beriberi neuropathy, characterized by high-carbohydrate, low-thiamine diet, hard exercise, typical symptoms of beriberi (edema, cardiac enlargement, and neuropathy), and dramatic improvement after a single administration of vitamin B_1.[1]

In human beriberi neuropathy, there have been no previous studies by ultrastructural, histiometric, and teased-fiber methods. Axonal degeneration was distinctive in the myelinated fibers. In addition to the nonspecific features of axonal degeneration, there were unusual changes: accumulation of flattened sacs or tubuli in the axoplasm of large myelinated fibers in untreated patients (No. 1 and 2). In thiamine-deficient rats, similar accumulation of sacs was also recognized within the intramuscular nerves and the terminal axoplasmic expansions of neuromuscular junctions by Prineas,[2] and within the terminal buttons in the vestibular nuclei by Tellez and Terry.[11] These findings may be characteristic of the early axonal changes in thiamine-deficient states in man as well as in animals.

Some of the sacs often showed a tubular aspect resembling neurotubules, and were orientated with surrounding neurofilaments. Lampert et al[12] have demonstrated the continuity of neurofilaments with sacs accumulated in the axoplasm of vitamin E-deficient rats. Some of the sacs in the present cases may have been produced by dilation of neurotubules, but others came from increased endoplasmic reticulum. Branching sacs were also demonstrated by Prineas[2] in experimental thiamine-deficient rats.

In human beriberi neuropathy, axonal degeneration was marked in comparison with the changes in the myelin sheath, as in vincristine sulfate, alcohol, triorthocresyl phosphate, and acrylamide neuropathies.[11-15] Segmental demyelination and clear pictures of onion bulbs were exceptional. Bimodal distribution of fiber diameter in unmyelinated axons,[10] Bünger bands containing unmyelinated axons,[16] clusters of Schwann cell processes and thin myelinated axons,[8] and disproportionately short internodal lengths in teased myelinated fibers[5,6] all resulted from regeneration due to axonal or Wallerian degeneration. Prineas[17] showed dying-back degeneration in experimental thiamine-deficient rats. From the findings in sural nerve biopsy specimens alone, it cannot be concluded whether or not axonal degeneration in beriberi is of the dying-back type.

Early onion bulb formation and remyelination of large single fibers with redundant basement membranes

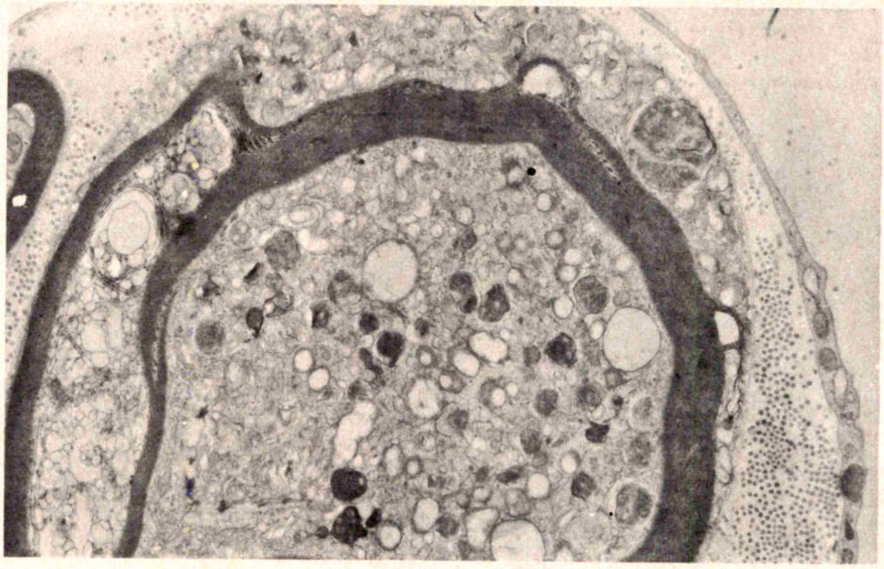
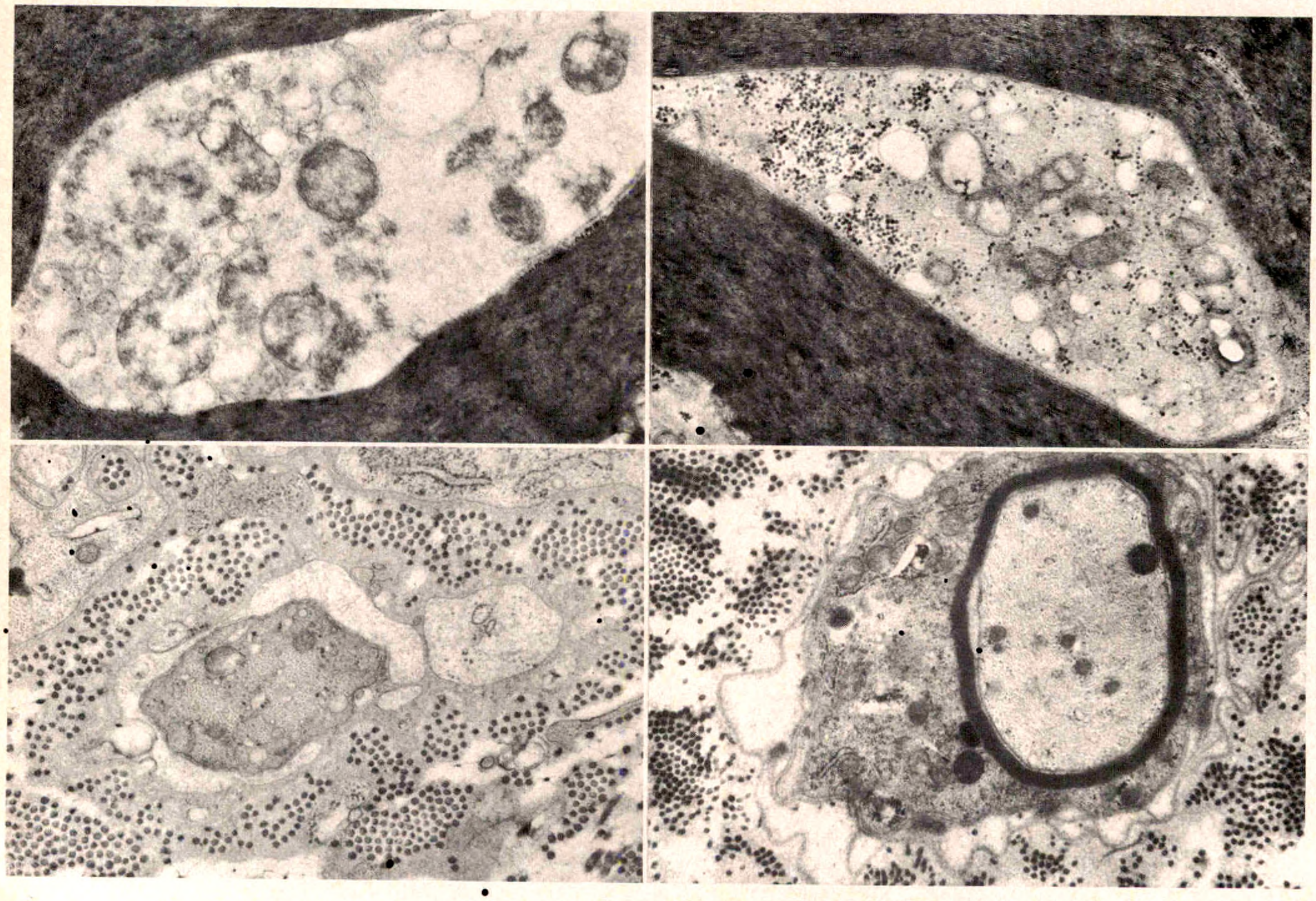


Fig 6.—Sural nerve in patient 2. Irregular sacs, vesicles, and small myelin figures occupy axoplasm and Schwann cell cytoplasm (original magnification, ×12,000).

Fig 7.—Dense floccular materials in axons (top left) and accumulation of glycogen granules and vesicles in axon (top right) in patient 2 (original magnification, ×9,800). Bottom left, Demyelinated axon with increased density surrounded by irregular Schwann cells and redundant basement membrane in patient 2 (original magnification, ×7,500). Bottom right, Remyelinated fiber with thin myelin sheath and redundant basement membrane in patient 8 (original magnification, ×5,000).



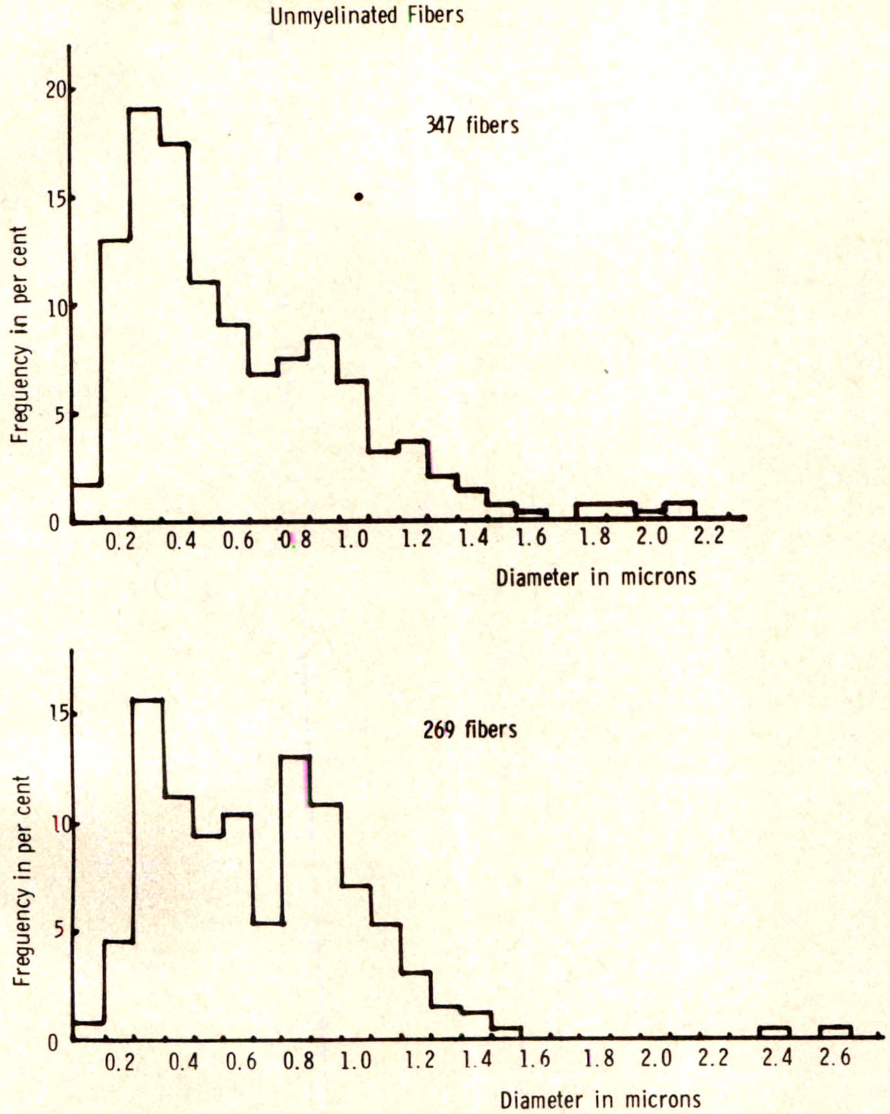


Fig 8.—Diameter frequency histograms of unmyelinated fibers showing bimodal distribution in patient 4 (top) and patient 8 (bottom).

(Fig 10), observed in patients 8 and 9, may be correlated with their relapsing course. Onion bulbs are said to be formed by repeated demyelination and remyelination,[18] or from degeneration and regeneration of axons.[19]

The atrophic axons denuded or enveloped only by Schwann cells and surplus basement membranes may represent demyelination induced by axonal degeneration, as postulated in uremic neuropathy by Dyck et al.[7]

The large myelinated fibers were more extensively affected than unmyelinated ones. Thiamine plays an important role in oxidative metabolism, and large fibers may be more sensitive to the inhibition of oxidative metabolism caused by thiamine deficiency. Fast axoplasmic transport is impaired by depressed oxidative metabolism,[20] and this may be correlated with the early changes in the neurotubules.

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Nonproprietary Name and Trademark of Drug

Vincristine sulfate—*Oncovin.*

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Electrophysiological Study of Anomalous Innervation of Intrinsic Hand Muscles

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• The collision technique was used to study the incidence of anastomosis between median and ulnar nerves in the forearm (Martin-Gruber anastomosis). A motor anastomosis from median to ulnar nerve was found in 57 (17%) of 328 unselected subjects. The anomaly was bilateral in 39 subjects (68%) and unilateral in 18, nine on the right and nine on the left. Both hypothenar and thenar muscles were tested in 77 of 96 hands with the anastomosis (right and left sides combined). Both muscle groups were innervated by the communicating fibers in 63 hands (82%). Anomalous innervation was limited to hypothenar muscles in 13 and to thenar muscles in one hand. In contrast to the high incidence of the anastomosis from median to ulnar nerve, crossover from ulnar to median nerve in the forearm was found in none of 303 subjects tested.

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Anatomical studies have demonstrated the frequent presence of a communication between median and ulnar nerves at the level of the forearm (Martin-Gruber anastomosis).[1-4] Clinical observations suggest that this communication is usually associated with anomalous innervation of the intrinsic hand muscles.[5-10] Awareness of this anastomosis is important in the evaluation of injuries as well as for accurate interpretation of conduction velocity determinations of median and ulnar nerves.[11-15] In the present study a simple electrophysiological technique has been used to study anomalies in the innervation of hypothenar and thenar muscles and its relation to the Martin-Gruber anastomosis. The incidence in a large-scale survey will be reported.

METHODS

Surface recording electrodes were placed on the hypothenar eminence. A stimulus of 0.1 msec in duration and of supramaximal intensity was delivered to the median nerve percutaneously at the elbow. In the absence of median to ulnar communication, the activity recorded in this setting is that of a volume-conducted potential (largely positive in polarity with a terminal negative deflexion)[15] originating in median innervated thenar muscles (Fig 1). The possibility of anomalous innervation was suggested if an early negative component was present superimposed on the volume-conducted potential. Compound action potentials from hypothenar muscles anomalously innervated by the communicating fibers, however, were not always clearly distinguishable from the volume-conducted potentials originating from median innervated thenar muscles.

The collision technique was used to separate these two types of responses by stimulating the median nerve both at the wrist and elbow (Fig 1). Normally, antidromically directed impulses from the distal stimulation would block, by collision, orthodromic impulses from the proximal stimulation in the same nerve, thus eliminating the muscle potentials resulting from the latter.[15-17] The orthodromic impulses traveling through the anastomotic branch to the ulnar nerve, however, would bypass the antidromic impulses. The compound action potential escaping collision, therefore, must originate in muscles anomalously innervated by the communicating fibers (Fig 1 and 2). By this means, it was also possible to assess the actual size of the anomalous response, which was clearly

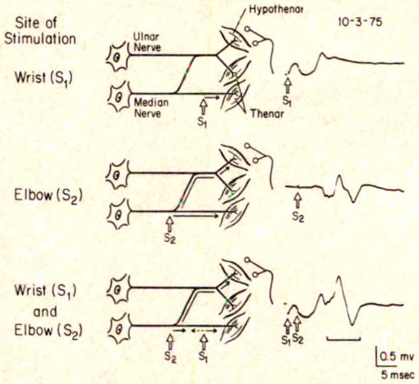

Fig. 1.—Median nerve was stimulated at sites indicated and muscle action potentials were recorded from hypothenar eminence. Top tracing shows volume-conducted potential from thenar muscles (U-shaped wave of positive polarity). In middle tracing, small negative potential is seen superimposed on volume-conducted potential. Bottom tracing shows anomalous response (bracket) clearly separated from volume-conducted potential when collision technique was used. Distal stimulus was given 4 msec before proximal stimulation.

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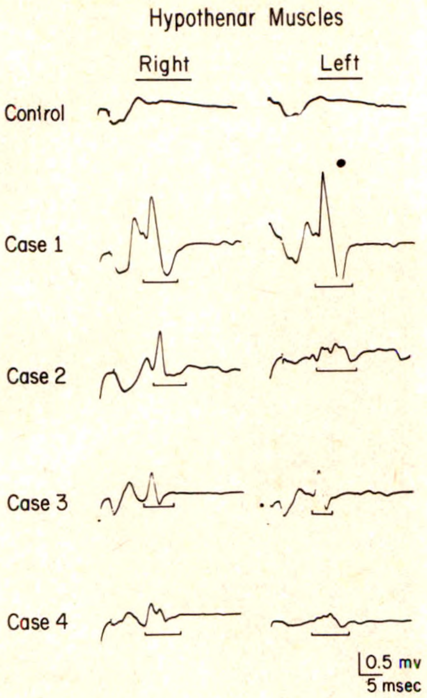
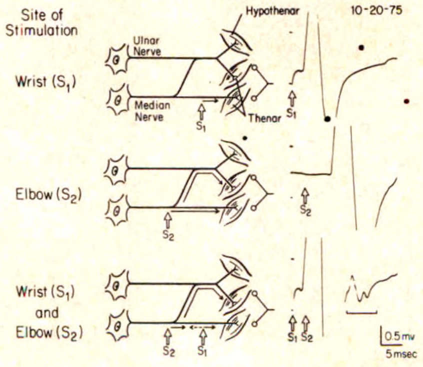


Fig 2.—Anomalous responses (brackets) from hypothenar muscles bilaterally in four cases. Median nerve was stimulated at both wrist and elbow (cf bottom tracing in Fig 1). Top tracings are from control subject with no anomaly. Initial positive waves are volume-conducted potentials from thenar muscles activated by distal stimulation.

Fig 3.—Median nerve was stimulated as in Fig 1 and muscle action potentials were recorded from thenar eminence (cf Fig 1). Top and middle tracings show compound action potential from median innervated thenar muscles. In middle tracing, this potential overlapped with anomalous response mediated by anastomosis. In bottom tracing, these two muscle potentials were separated by collision technique to detect anomalous response (bracket). Distal stimulus was given 4 msec before proximal stimulation.

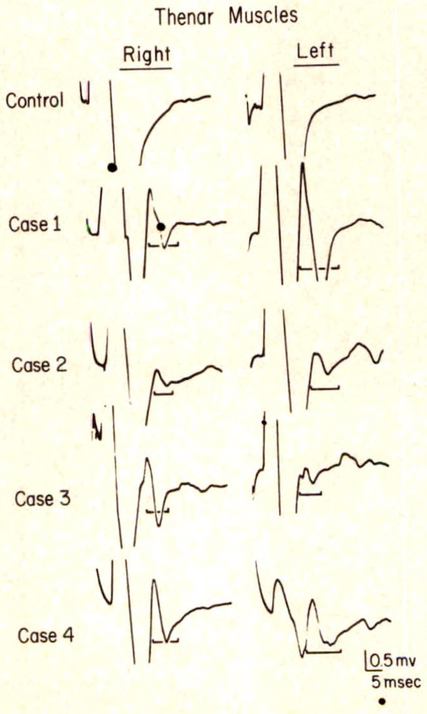


separated from the volume-conducted potential.

To determine whether thenar muscles were also innervated by fibers forming the median to ulnar anastomosis, the median nerve was stimulated at the elbow as well as at the wrist with recording electrodes on the thenar eminence (Fig 3). Only the impulses transmitted from the median to ulnar nerve along the anastomosis would bypass the antidromic activity from the wrist, activating ulnar innervated thenar muscles. Of course, the distal stimulation itself elicited an action potential in median innervated thenar muscles. For detection of an anomalous response, therefore, it was necessary to avoid as much as possible overlap of these two muscle potentials. This was in part accomplished by delivering the stimulus at the wrist a few milliseconds before the stimulation at the elbow (Fig 3). The time interval between the two stimuli was chosen such that the antidromic impulse resulting from the distal stimulation had not yet reached the proximal site of stimulation at the time the proximal shock was delivered. Otherwise, the nerve impulses produced by proximal stimulation would escape antidromic collision even in the absence of an anomalous route of transmission. Because of this limitation, complete separation of these two muscle potentials was not always achieved (Fig 4).

Similarly, communication from ulnar to median nerve in the forearm was looked for by stimulating the ulnar nerve both at the wrist and elbow, and recording from the thenar eminence. In this setting, the orthodromic impulses mediated by the anastomosis to the median nerve would bypass the antidromically directed impulses in the ulnar nerve. Only in the presence of communicating fibers, therefore, would proximal stimulation activate anomalously innervated thenar muscles.

Fig 4.—Anomalous responses (brackets) from thenar muscles bilaterally in same four patients shown in Fig 2. Median nerve was stimulated at both wrist and elbow (cf bottom tracing in Fig 3). In each tracing, initial portion of anomalous response is buried in terminal portion of compound action potential of median innervated thenar muscles activated by distal stimulation. Because of this overlap, a small anomalous response may have escaped detection despite use of collision technique. Top tracings are from control subject with no anomaly. Late potentials appearing after anomalous responses are F waves.



RESULTS

All patients referred for electrical studies of median or ulnar nerve between July 1 and Dec 31, 1975, were tested bilaterally. Patients were excluded from the study only if advanced disease of the peripheral nerve precluded accurate recording of compound muscle action potentials. There were 656 hands studied from 328 subjects, 155 males and 173 females, ranging in age from 6 to 91 years.

Electrical signs consistent with the presence of anastomosis from median to ulnar nerve were found in 57 subjects (17%), 27 males and 30 females. The anomaly was bilateral in 39 subjects (68%) and unilateral in 18, nine on the right and nine on the left. Innervation of both hypothenar and thenar muscles was tested in 77 of 96 hands with the anastomosis (right and left sides combined). Both muscle groups were innervated by the communicating fibers in 63 hands (82%). Anomalous innervation was limited to hypothenar muscles in 13 and to thenar muscles in one hand. In the remaining 19 hands tested early in the study, possible innervation of the thenar muscles by the communicating fibers was not evaluated. Electrical evidence of crossover from ulnar to median nerve was found in none of 303 patients tested.

In 89 hands with the median-to-ulnar anastomosis the amplitude of the anomalous response of the hypothenar muscles was 0.93 ± 0.65 mV (mean ± SD). In the same subjects, the compound muscle action potential elicited by supramaximal stimulation of the ulnar nerve at the wrist was 12.3 ± 4.0 mV. The amplitude ratio between these two muscle action potentials was calculated to determine the magnitude of anomalously innervated portion of the hypothenar muscles in individual hands. The average ratio was 7.9 ± 5.2% (mean ± SD), although it was as high as 26.1% in one subject and 22.9% in another.

COMMENT

Potentials recorded from hypothenar eminence after median nerve stimulation may be volume-conducted from median innervated distant muscles or secondary to anomalous activation of hypothenar muscles by the stimulated nerve.[11-15] Distinction between these two possibilities is sometimes difficult despite the characteristic contour of the volume-conducted potential in the majority of subjects. Volume-conducted potentials, however, should remain essentially unchanged whether the median nerve is stimulated at the wrist or at the elbow, since the same group of intrinsic hand muscles is activated in either case. More importantly, fibers escaping collision can be considered to have taken an anomalous route proximal to the distal site of stimulation, as shown in Fig 1 and 3.

Using the aforementioned criteria, we demonstrated that fibers forming part of the median nerve trunk left it in the forearm and joined the ulnar nerve proximal to the wrist to innervate part of the hypothenar muscles. Furthermore, recording from the thenar eminence, it was shown that those fibers escaping collision often participated in the innervation of muscles in the radial half of the hand as well. Adjusting the site and intensity of the stimulus delivered at the elbow, we were often able to stimulate the anomalous fibers maximally, but selectively, without activating the median nerve proper. This observation suggests that the nerve fibers forming the anastomosis are grouped together in a separate bundle rather than scattered within the median nerve. Although we do not have anatomical data on our patients to substantiate these electrophysiological findings, we believe that they represent the functional correlate of the median to ulnar anastomosis in the forearm. In a group of patients with this anastomosis studied with needle electrodes after blocking the ulnar nerve with local anesthetics, Mannerfelt[3] found that the anastomosing fibers supplied the first dorsal interossei and adductor pollicis muscles on the radial side and the abductor digiti minimi on the ulnar side of the hand. Our findings correlate well with his although, using surface electrodes, we were unable to identify individual muscles receiving their motor supply from the anastomosing fibers.

In agreement with previous anatomical studies,[1-4] the present electrophysiological data verify a high incidence of the median to ulnar anastomosis in an unselected population. Our findings clearly indicate that the communicating fibers frequently innervate both hypothenar and thenar muscles and that, when present, the anomaly tends to be bilateral. In our subjects, motor communication in the forearm was exclusively from median to ulnar nerve: we found electrical signs of ulnar to median motor communications in none of our subjects. This is consistent with the phylogenetic origin of this anastomosis, as has been previously suggested.[18,19]

The collision technique is noninvasive and simpler than procaine nerve block employed by others[10,12] to corroborate the presence of the anastomosis. This simple method is of practical value not only in evaluating anomalous innervation of intrinsic hand muscles but also in improving the latency measurements by blocking unwanted nerve impulses in the presence of the anastomosis.[15]

The Neurosensory Center is supported by program project grant NS-03354 from the National Institute of Neurological Diseases and Stroke. This investigation was supported in part by a grant from the National Multiple Sclerosis Society.

Maurice W. Van Allen, MD, reviewed the article. David Walker, MSEE, provided electroengineering assistance. Sheila Mennen, Joanne Nahnsen, and Cindy Fouke gave technical assistance.

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Brief Communication

Peripheral Nerve Involvement in Hunter Syndrome (Mucopolysaccharidosis II)

Thomas R. Swift, MD, Thomas F. McDonald, PhD

• A 20-year-old man with confirmed Hunter syndrome had entrapments of median and ulnar nerves. Sural nerve biopsy specimen revealed clear, lamellated, and granular inclusions in Schwann cells, fibroblasts, and perineurial cells. The clear inclusions are believed to represent storage of mucopolysaccharide, and the zebra bodies, ganglioside. Focal alterations in myelin were found, associated with moderately dense granular inclusions. Following carpal tunnel release operations, the patient experienced dramatic relief of symptoms.

***(Arch Neurol* 33:845-846, 1976)**

Hunter syndrome, a sex-linked recessive trait, is characterized by short stature, coarse features, large head, deafness, skeletal deformities, cardiac abnormalities, protuberant abdomen with hepatosplenomegaly and umbilical hernia, intellectual impairment, skin lesions, and other features.[1] Affected individuals store large amounts of acid mucopolysaccharides (AMP) in the tissues and excrete them in the urine.[1] The enzyme L-iduronosulfate sulfatase, which normally acts to degrade AMP, is deficient in such patients.[2]

Peripheral nerve involvement in Hunter syndrome has been described by McKusick[1] and by Miner and Schimke[3] without electrophysiologic or neuropathologic data. Recently, three patients have been reported with peripheral nerve entrapments who excreted large amounts of AMP and had biochemical defects but no clinical signs that were characteristic of Hunter syndrome.[4]

This report describes the clinical, electrical, and neuropathologic features of a patient with classical Hunter syndrome and multiple peripheral nerve entrapments.

REPORT OF A CASE

A 20-year-old man was referred because his hands had been numb for five months. The patient's birth had been normal; however, at several years of age, short stature, protuberant abdomen, coarse facies, and deafness were noted.

Physical examination revealed a short (151 cm), obviously deformed man, with coarse facies, large tongue, protuberant abdomen, and skeletal deformities that were characteristic of Hunter syndrome.[1]

The head circumference was 58 cm. Mentation appeared to be dull normal. Weschler Adult Intelligence Scale disclosed a full-scale intelligence quotient of 93.

Cranial nerve functions were normal except for blurring of the optic disks and conductive hearing loss. Palmar abduction of both thumbs was weak. Muscle stretch reflexes were hyperactive and bilateral Babinski signs were present. There was loss of pinprick and touch sensation in the first four digits of the right hand on the palmar surface, splitting the fourth digit. On tapping the wrists, the patient developed electrical sensations in the fingers.

Results of routine laboratory studies were normal. Chest, skull, and spine roentgenograms revealed osseous changes characteristic of Hunter syndrome.[1]

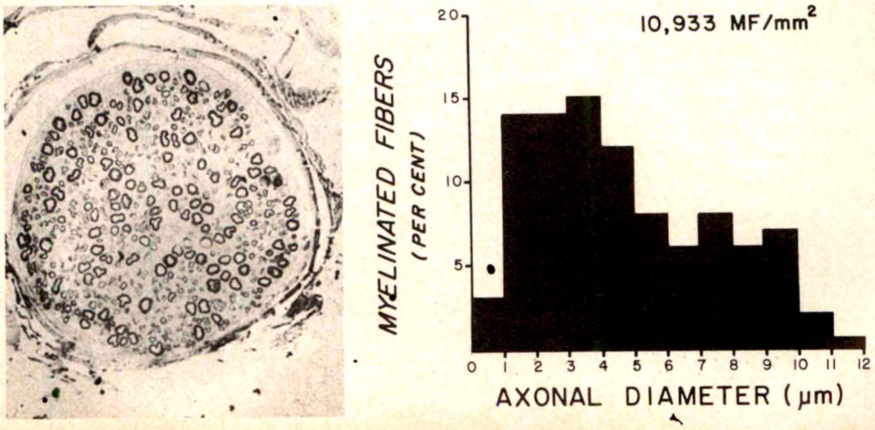
Electroencephalogram showed bilateral slow wave activity at 3 hertz, of greater amplitude on the right side. Computerized axial tomography of the head gave normal results, showing no ventricular enlargement.

Twenty-four hour urine collection revealed markedly elevated AMP excretion. Dermatan and heparan sulfate were estimated at 30% and 60%, respectively, with 10% of chondroitin 6-sulfate, consistent with Hunter syndrome.[1] The patient's serum was deficient in the enzyme L-iduronosulfate sulfatase, characteristic of Hunter syndrome.[2]

Results of motor and sensory nerve conduction studies were normal except for right ulnar conduction velocity of 42 meters/second (normal, > 48 meters/second) and median motor distal latency times of 5.7 and 6.0 msec, right and left, respectively (normal, < 4.5 msec). Right median sensory distal latency was 4.8 msec (normal, < 3.7 msec), and on the left it was not obtainable.

The patient underwent bilateral carpal tunnel release operations. The median nerves appeared swollen for several centimeters proximal to and within the carpal tunnel. Following both operations, the patient experienced dramatic relief of symptoms and improvement in results of electrophysiologic tests.

Fig 1.—Left, In fascicle of sural nerve, myelinated fibers appear normal and perineurium is not thickened (osmium tetroxide, ×660). Right, Total myelinated fiber (MF) counts per square millimeter fascicular area. Normal bimodal size distribution of myelinated fibers is present.



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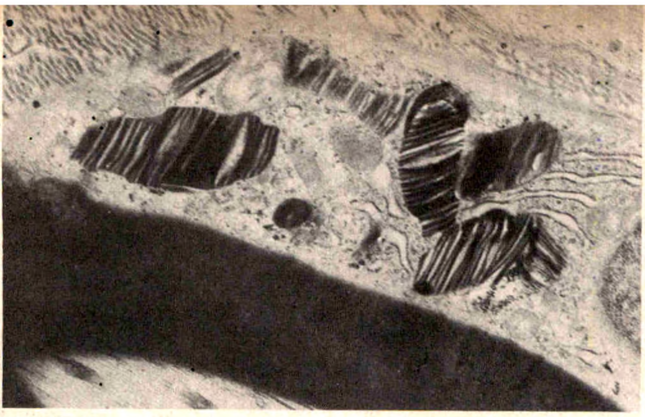

Fig 2.—Zebra bodies in cytoplasm of Schwann cell (osmium tetroxide, ×15,000).

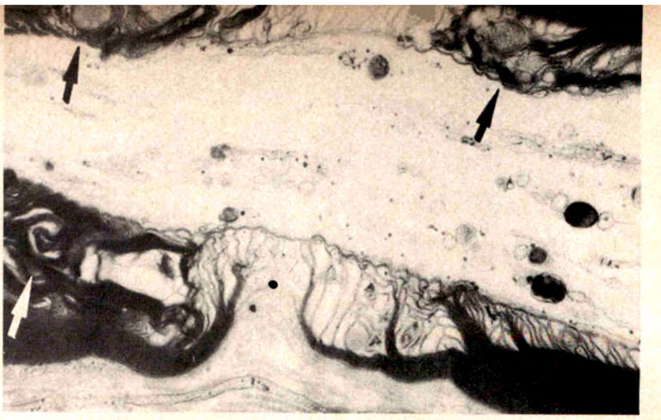

Fig 3.—Granular inclusions in Schwann cell cytoplasm in area of node of Ranvier (black arrows). Abnormal formations of myelin are also present (white arrow) (osmium tetroxide, ×22,000).

RESULTS

Neuropathologic Findings

A biopsy of the right sural nerve was performed. Fascicles examined with light microscopy revealed 10,933 myelinated fibers per square millimeter of fascicular area, which is in the normal range,[5] with a normal bimodal size distribution (Fig 1).

Results of electron microscopic examination revealed multivacuolated endoneurial fibroblasts, characteristic of mucopolysaccharidoses.[1] Perineurial cells were similarly involved. Schwann cells contained lamellar inclusions, "zebra bodies," consisting of elongate structures with the lamellae running vertical to the long axis (Fig 2). Another type of inclusion commonly found in Schwann cell cytoplasm was bordered by a single membrane and contained moderately dense granules. Such inclusions were present in large numbers in incisural and nodal cytoplasm of Schwann cells, and frequently were observed in areas of altered myelin (Fig 3). Most axons appeared normal, but a few appeared shrunken with increased numbers of organelles. Endoneurial capillaries were normal. Reynaut corpuscles were not observed.

COMMENT

This study shows for the first time that a substantial amount of abnormal storage material is present in a large peripheral nerve in Hunter syndrome. It has been established that the material stored in the clear vacuoles is AMP.[6] Fibroblasts are chiefly affected, possibly because these cells normally secrete AMP,[7] and the enzyme deficiency (L-iduronosulfate sulfatase) prevents its degradation. There is biochemical evidence to suggest that zebra bodies and cytoplasmic membranous bodies contain ganglioside.[8] In our study, zebra bodies were chiefly in Schwann cells, possibly because these cells are involved in myelin metabolism, and a small percentage of normal peripheral nerve myelin is ganglioside of the same type observed in the central nervous system.[9]

The clear and lamellated inclusions that we found appear identical to those found in rectal ganglion cells in Hunter syndrome[10] and in dermal nerves in many mucopolysaccharidoses.[11-13]

The nature of the third type of inclusion (moderately dense granules) observed in Schwann cells and occasionally in fibroblasts is unknown. Similar inclusions have been described in cerebral biopsy specimens of patients with mucopolysaccharidoses,[8] in variant O form of metachromatic leukodystrophy,[14] and in mitral valve leaflet in Hunter syndrome.[15] They, too, are believed to contain ganglioside.[8] We were impressed with the constant presence of these granules in the areas of myelin changes, especially at Schmidt-Lantermann clefts and nodes of Ranvier. The presence of granules conceivably could be detrimental to circulatory or other postulated functions of the clefts.[16]

Patients with mucopolysaccharidoses develop nerve entrapments, the carpal tunnel being by far the most common site.[1,3,4] It is believed that this is caused by extrinsic pressure from thickened surrounding tissues. It is uncertain whether the abnormal storage material we have demonstrated in nerve is an additional factor contributing to entrapment.

The enzyme assay was performed by Elizabeth Neufeld, PhD, and Inge Liebaers, PhD, National Institutes of Health, Bethesda, Md.

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Letters and Clinical Notes

Electrode Implantation and Stimulation in the Hippocampus

To the Editor.—Dr Salcman (*Arch Neurol* 33:215, 1976) commented on our article (*Arch Neurol* 32:98, 1975) describing the response of enzymes important to brain metabolism after electrode implantation and electrical current application in the hippocampus. He suggested that the electrical measurements were too low and that techniques were inadequately described to enable workers to approach the problem from a different perspective.

The electrical current levels reported were similar to those used by others.[1,2] The current selected was routinely capable of polarizing the hippocampus, which is well known to have a low electrical threshold; similarly, the auditory nerve and cochlea are also known to have a low electrical threshold.[3,4] Procedures of this hippocampal study were not intended to be translatable to the cortex or cerebellum. For such studies, a different species, method, and experimental technique are clearly desirable. It is an enigma that Dr Salcman's calculations were in microcuries per square centimeter when no radiation was referred to in our article. Perhaps he intended this as the charge density, which should be given in microcoulombs per square centimeter. A rich literature exists to suggest that the power density in watts per square centimeter or charge per phase or current density in milliamperes per square centimeter may be more significant descriptors of damage secondary to application of electrical current.[3-6] Based on the size of the electrode and the stated factors, a current density of approximately 240 mamp/sq cm at 0.1-millisecond duration would be passed to the electrode tip. In our experience, this level is sufficient for polarization of hippocampal nerve cells. Furthermore, the currents passed from the typical laboratory generator were unidirectional. It is doubtful that a measurement of impedance would provide an estimate of the electrode tip area. The wire gauge was clearly stated in the "Methods" section. The method of implantation is typical of techniques routinely used in the experimental laboratory and was therefore the technique of choice in this experiment. The enzyme response attributed to disturbance of the tissue by electrode implantation was extremely high. The enzyme reaction to tissue damage masked any possible changes attributable to electrical current. The relevance of factors mentioned by Dr Salcman became of secondary importance in the light of the enzyme response to injury. It was our view that a sequence of experiments on increasing the current density or electrical charge to a maximum within an optimal range for the rat hippocampus would yield no further information beyond that reported, and so experiments using higher electrical power were therefore abandoned. It is regrettable that Dr Salcman misunderstood the intent of our research, which was primarily designed to study histological trauma secondary to electrode implantation in a typical laboratory experiment. We are, however, grateful for the points in his letter that suggest additional studies are necessary to delineate trauma secondary to electrode studies on surface and in depth structures of the brain requiring considerably more electrical power and different electrode arrays and methods.

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Dr Salcman's letter was sent on to Dr Robinson, but regrettably did not reach him. We are pleased to publish his reply.—Ed.

Maturational Arrest

To the Editor—Reports on the skeletal muscle pathology in infantile myotonic dystrophy (IMD) may be few, as Drs Sarnat and Silbert remark (*Arch Neurol* 33:466, 1976). Nevertheless, in the face of this paucity they overlooked or omitted our report[1] in which biopsy specimens from four patients who had been severely affected in the neonatal period were obtained at 13, 18, and 22 months, and 6 years of age. It is instructive to compare the reports. The muscle fibers studies by Sarnat and Silbert were all obtained before the third week of life. They showed a striking prevalence of central nuclei and deficient differentiation into histochemical fiber types. These findings are indeed interpretable as maturational retardation, though not necessarily "arrest." In our patients clinical improvement had occurred, as so often happens in IMD, after the first few months. Central nuclei were somewhat more numerous than normal, and even the "sarcolemmal" nuclei tended to have a few myofilaments situated peripheral to them. Abnormal acid phosphatase-positive sites were prominent in many muscle fibers in these patients. They are quite distinct from the motor end-plates that have acid phosphatase activity in normal infants. They apparently corresponded to dense core tubules. By the age of 5 years they seem to disappear. Data are unfortunately not available from the study of Sarnat and Silbert as to whether they are found in the neonatal period. Other features in our biopsy studies indicated a transition towards the morphological picture of adult myotonic dystrophy: relative smallness of the type I fibers, and, in one patient at age 18 months, both ring myofibrils and sarcoplasmic masses. Our findings do not support the idea of a persistent impairment of maturation in IMD.

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1. Karpati G; Carpenter S, Watters GV: Infantile myotonic dystrophy: Histochemical and electron microscopic features in skeletal muscle. *Neurology* 23:1066-1077, 1973.

In Reply.—I regret that the report of Karpati et al ("Infantile Myotonic Dystrophy," *Neurology* 23:1066-1077, 1973) was inadvertently overlooked in our review. Their article indeed is relevant and important to understanding the range of infantile myotonic dystrophy.

Their patients differed from ours in having minimal or no arthrogryposis at birth and in surviving. The assumption that the muscle fibers in their patients had been less mature at birth, and had progressed in development during the months and years before muscle biopsies were performed, is not necessarily a justified conclusion. We emphasized in our patients that the state of immaturity of the muscle corresponded to the degree of clinical involvement; the least mature muscles were those associated with arthrogrypotic joints, and other muscles were minimally involved both clinically and pathologically. We chose to regard the pathologic condition of severely involved muscles as maturational arrest because all stages of development, from satellite cell and myoblast to mature myocyte, were represented within a given muscle. Whether maturation in time actually takes place will only be known when serial biopsy specimens of the same muscle in the neonatal period and in later childhood are performed in those infants who survive.

Although histochemical incubations for acid phosphatase were not performed in our patients, our electron micrographs demonstrated longitudinally oriented tubules, a fetal feature that probably corresponds to the ultrastructural substrate of the "dense cores" reported by Karpati et al. Their electron micrographs showed similar structures.

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News and Comment

Clinical Electrodiagnosis of Neuromuscular disease.—New York University Post-graduate Medical School will offer "Clinical Electrodiagnosis of Neuromuscular Disease" on Dec 8, 1976. Under the direction of Drs Howard A. Rusk and Joseph Goodgold this continuing medical education offering meets the criteria for 30 hours of credit in category I for the Physician's Recognition Award of the American Medical Association.

For details, write or phone Office of the Associate Dean, Registration Department, New York University Post-Graduate Medical School, 550 First Ave, New York, NY 10016; (212) 679-3200, X4207.

Annals of Neurology.—Beginning in January 1977 the *Annals of Neurology* will begin publication. *ANNALS OF NEUROLOGY* is the officially sponsored publication of the American Neurological Association, and its contents will be devoted to clinical papers and reviews, as well as to original papers and reviews on experimental subjects that relate to the human nervous system or human neurological problems. Editorials, letters, and notes will be welcomed and can be submitted to Dr. Fred Plum, Editor, *ANNALS OF NEUROLOGY*, New York Hospital-Cornell Medical Center, New York, NY 10021. The publisher is Little, Brown & Co, 34 Beacon St, Boston MA 02106. Correspondence concerning subscription can be sent to the Boston address.

Dyslexia—Current Developments.—The Page and William Black Post-Graduate School of Medicine of the Mount Sinai School of Medicine (CUNY) announces a post-graduate course, cosponsored with The New York State Branch of The Orton Society, Inc., entitled "Dyslexia—Current Developments." It will be given on Jan 22, 1977, at the Mount Sinai Medical Center in New York City, under the direction of Dr Virginia Lubkin, and will offer category I credit, AMA Physician's Recognition Award.

Apply to Director, The Page and William Black Post-Graduate School of Medicine, Mount Sinai School of Medicine, Fifth Avenue and 100th Street, New York, NY 10029.

Third Annual Richard Lende Winter Neurosurgery Conference.—The Third Annual Richard Lende Winter Neurosurgery Conference will be held Feb 5 through 10, 1977, in Snowbird, Utah. Information may be obtained from M. Peter Heilbrun, MD, Division of Neurological Surgery, University of Utah Medical Center, 50 N Medical Dr, Salt Lake City, UT 84132.

Rocky Mountain Neuro-ophthalmology Course.—The Third Annual Rocky Mountain Neuro-ophthalmology Course will be held Feb 9 through 11, 1977, at Tamarron, Durango, Colo. For further information write to Thomas J. Carlow, MD, c/o Neuro-ophthalmology Course, Department of Neurology, University of New Mexico, 2211 Lomas Blvd NE, Albuquerque, NM 87131.

Topics in Neurology, 1977.—This course, which is to be given Feb 28 through March 2, 1977, at The Johns Hopkins Medical Institutions, will provide new information about the basic mechanisms of the disease and the diagnosis and management of clinical problems. Special areas covered this year will include neuro-oncology, neurotransmitters, cerebrovascular disease, and new concepts in neurology. The registration fee is $200 for 22 hours of category 1 credit.

Further information may be obtained from the Office of Continuing Education, The Johns Hopkins Medical Institutions, Rm 17, Turner Auditorium, 720 Rutland Ave, Baltimore, MD 21205.

Fifth Annual Neurologic Education Workshop.—The newly formed Society for Neurologic Education is interested in the techniques and goals of education and wishes to provide a vehicle for interested persons to share ideas and cooperatively apply to neurologic education the same benefits as come from sharing scientific information and investigation in other fields. The Society will help to present a special course on neurologic education at the next meeting of the American Academy of Neurology in Atlanta in April 1977. The program will consist of formal papers and workshop-type activities on neurologic teaching techniques, goals, resources, and forms of evaluation.

Further information about the Society and the course may be obtained from the Chairman, James Q. Miller, MD, Department of Neurology, School of Medicine, University of Virginia Medical Center, Charlottesville, VA 22901.

Problem Solving in Strabismus.—The Bascom Palmer Eye Institute, University of Miami School of Medicine, and the Southern Region of the American Association of Certified Orthoptists will present a continuing education course entitled "Problem Solving in Strabismus" on May 1 through 4, 1977, at the Royal Biscayne Hotel, Key Biscayne, Miami, Fla. The program is accredited by the Council on Medical Education of the American Medical Association. For further information, write to Bascom Palmer Eye Institute, PO Box 520875, Miami, FL 33152.

New Chairman of Neurology at Chicago Medical School.—Dr Charles E. Morris has been appointed professor and chairman of the Department of Neurology at the University of Health Sciences/Chicago Medical School. He is also chief of the Neurology Service at the North Chicago Veterans Administration Hospital. Dr Morris was formerly professor of neurology and medicine at the University of North Carolina at Chapel Hill.

Postdoctoral Fellowships.—The Clinical Neuroscience Research Center of the Departments of Neurology and Neurosurgery at the University of Virginia School of Medicine offers National Institutes of Health fellowships for postdoctoral training in developmental neurology to qualified applicants holding an MD, PhD, or equivalent degree. The program is designed to provide interdisciplinary training opportunities in neuroanatomy, electron microscopy, histochemistry, neurophysiology, neural modeling, neurochemistry, and neuropharmacology as part of basic research and neuromuscular disease. Immediate openings exist for three candidates at stipends ranging from $10,000 to $14,000. Send applications and curriculum vitae to Dr Norman H. Bass, Department of Neurology, University of Virginia School of Medicine, Charlottesville, VA 22901.

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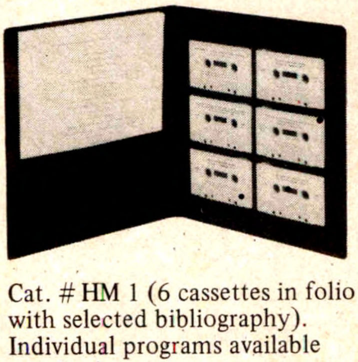

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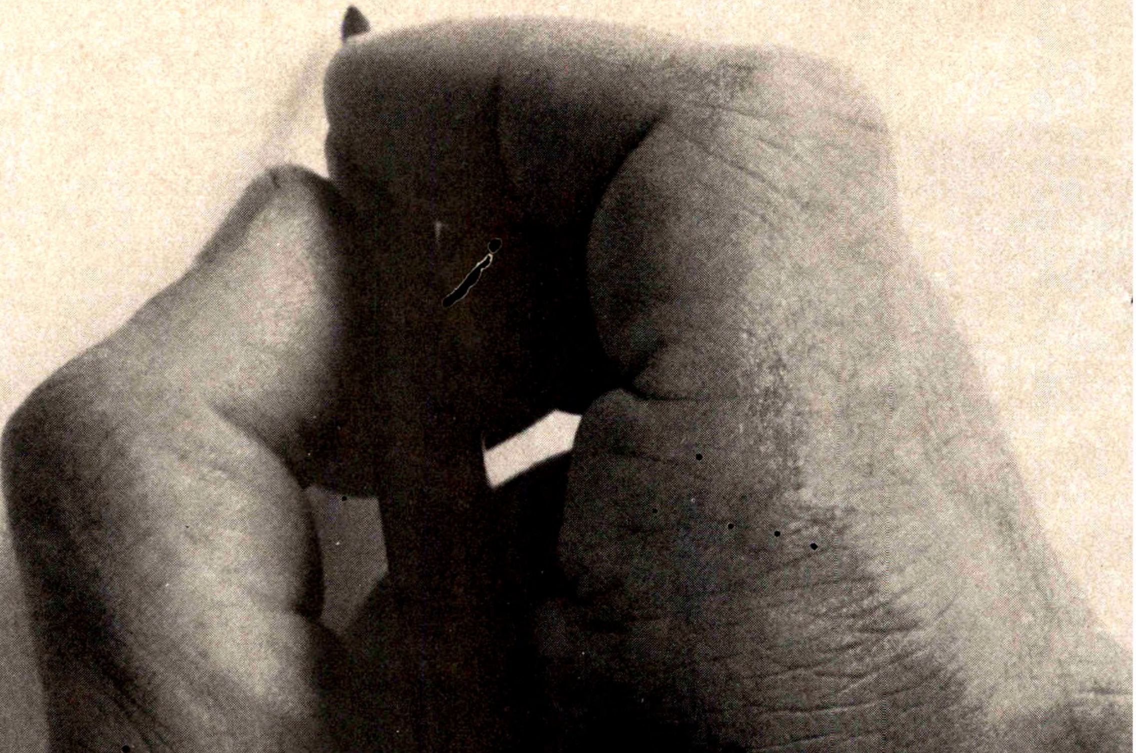

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(except tardive dyskinesia)

often permits needed chemotherapy to continue by controlling drug-induced extrapyramidal manifestations such as: *tremor, akathisia, motor restlessness, muscular rigidity, drooling, dystonic reactions.*

In some patients, however, the phenothiazine dosage may have to be reduced or discontinued. After one or two weeks, COGENTIN should be withdrawn to determine the continued need for it.

When given concomitantly with phenothiazines or other drugs with anticholinergic activity, patients should be advised to report gastrointestinal complaints promptly; paralytic ileus, sometimes fatal, has occurred in patients taking anticholinergic-type antiparkinsonism drugs, including COGENTIN, in combination with phenothiazines and/or tricyclic antidepressants.

Contraindications: Children under three years of age; use cautiously in older children.

Warnings: Safe use in pregnancy not established. May impair mental and/or physical abilities required for performance of hazardous tasks, such as operating machinery or driving a motor vehicle. When given concomitantly with phenothiazines or other drugs with anticholinergic activity, patients should be advised to report gastrointestinal complaints promptly; paralytic ileus, sometimes fatal, has occurred in patients taking anticholinergic-type antiparkinsonism drugs, including COGENTIN, in combination with phenothiazines and/or tricyclic antidepressants.

Precautions: Because of cumulative action, continued supervision is advisable. Closely observe patients with tendencies to tachycardia and those with prostatic hypertrophy. Dysuria may occur, but rarely becomes a problem. Large doses may cause complaints of weakness and inability to move particular muscle groups, requiring dosage adjustment.

Mental confusion and excitement may occur with large doses, or in susceptible patients; visual hallucinations reported occasionally. May intensify mental symptoms when used to treat extrapyramidal disorders due to neuroleptic drugs (e.g., phenothiazines) in patients with mental disorders; in such patients, increased doses of antiparkinsonian drugs can precipitate toxic psychosis; observe patients carefully, especially at the beginning of treatment or if dosage is increased. Tardive dyskinesia may appear in some patients on long-term therapy with phenothiazines and related agents, or may occur after therapy with these drugs has been discontinued; antiparkinsonism agents do not alleviate symptoms of tardive dyskinesia, and in some instances may aggravate them. COGENTIN is not recommended in tardive dyskinesia.

May produce anhidrosis; give with caution during hot weather, especially to the old, the chronically ill, the alcoholic, those who have central nervous system disease, those who do manual labor in a hot environment, and those with disturbances in sweating. If anhidrosis appears, reduce dosage so that ability to maintain body heat equilibrium is not impaired. Occurrence of glaucoma is a possibility; probably should not be used in angle-closure glaucoma.

Adverse Reactions: Adverse reactions may be anticholinergic or antihistaminic. Dry mouth, blurred vision, nausea, nervousness may develop. If dry mouth causes difficulty in swallowing or speaking, or loss of appetite and weight, reduce dosage, or discontinue drug temporarily. Vomiting occurs infrequently and may be controlled by temporary discontinuation, followed by resumption at a lower dosage. Constipation, numbness of the fingers, listlessness, and depression may develop. Occasionally, an allergic reaction, e.g., skin rash, develops; sometimes this can be controlled by reducing dosage, but occasionally requires discontinuation.

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addendum

Facts about dosage schedules of COGENTIN (Benztropine Mesylate | MSD)

In treating extrapyramidal symptoms due to neuroleptic drugs, such as phenothiazines and butyrophenones, the recommended dosage of COGENTIN is 1 to 4 mg once or twice a day orally or parenterally. Dosage must be individualized according to the need of the patient. Some patients require more than recommended; others do not need as much. The tablet form should be used when patients are able to take oral medication.

When extrapyramidal symptoms develop soon after initiation of treatment with neuroleptic drugs, they are likely to be transient. One to 2 mg COGENTIN orally two or three times a day usually provides relief within one or two days. After one or two weeks, COGENTIN should be withdrawn to determine the continued need for it. If symptoms recur, COGENTIN can be reinstituted.

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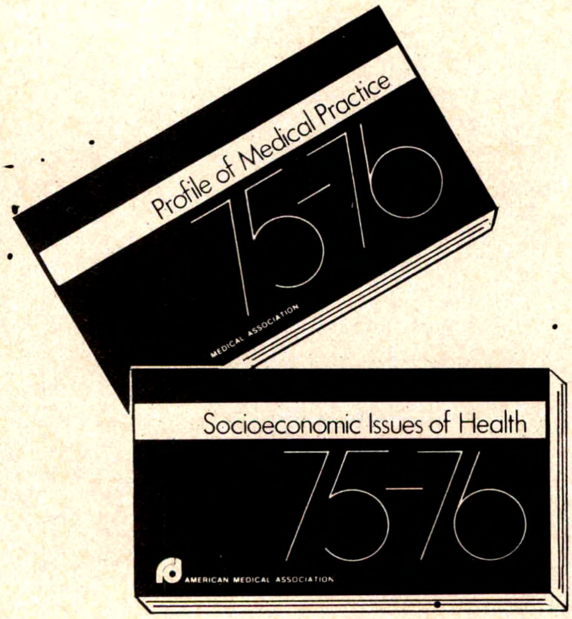
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The Problem...

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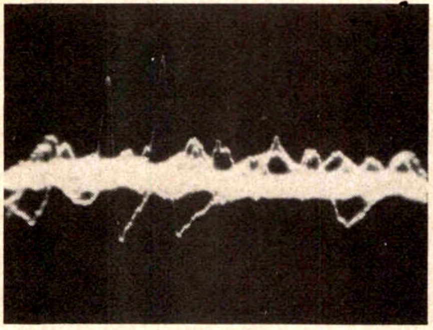
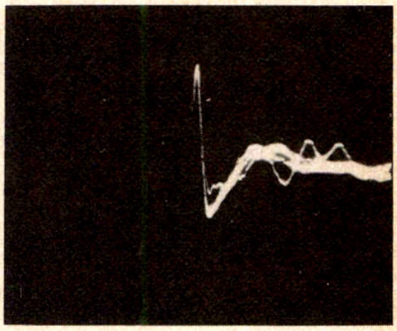
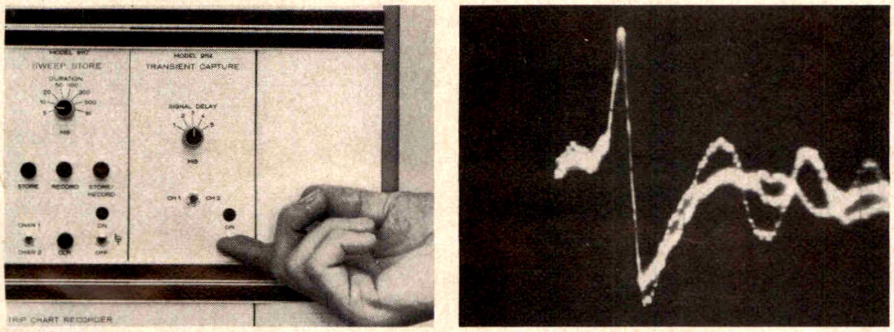


You can let the scope free run, but the MUP is only caught a few times in many sweeps.

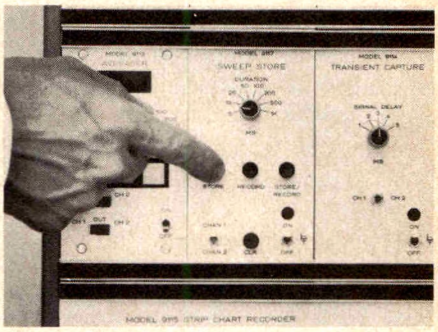


Or you can trigger off of the MUP. But then you lose the wave form occurring before trigger level is reached.

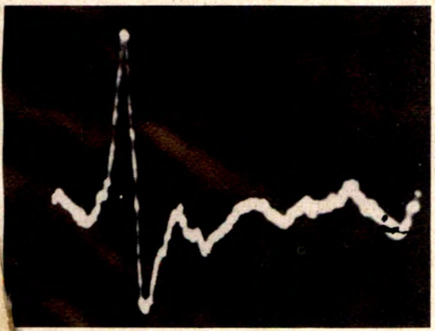
The Life-Tech solution...



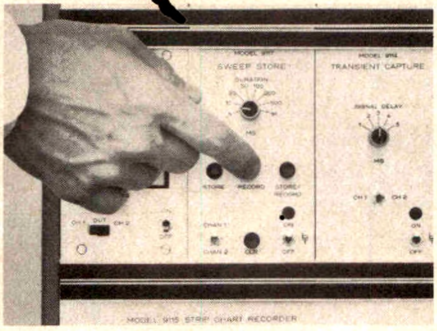
Turn on the transient capture module. Now you can trigger off of the MUP, yet display the entire signal (because the transient capture delays the displayed signal but not the triggering signal).



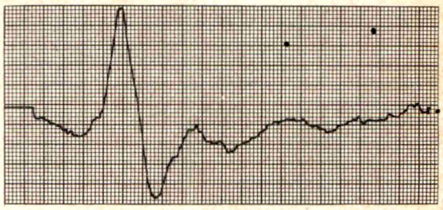
Push the "STORE" button.



One of the sweeps is frozen and can be spected at leisure.



Push the "RECORD" button.



Obtain a permanent graphic record of the frozen waveform on standard EKG chart paper.

The Life-Tech EMG System carries a one-year warranty and is backed by a nationwide service-center network. For complete information, call or write.

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PROGRESS IN NEUROPATHOLOGY

VOLUME III

Edited by H. M. ZIMMERMAN, M.D.

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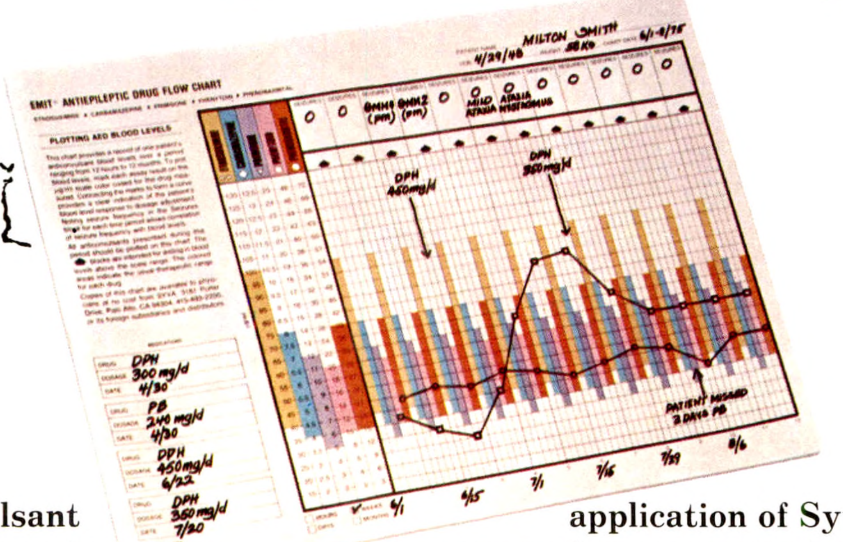
While every precaution is taken to insure accuracy, we cannot guarantee against the possibility of an occasional change or omission in the preparation of this index.

the epileptic map



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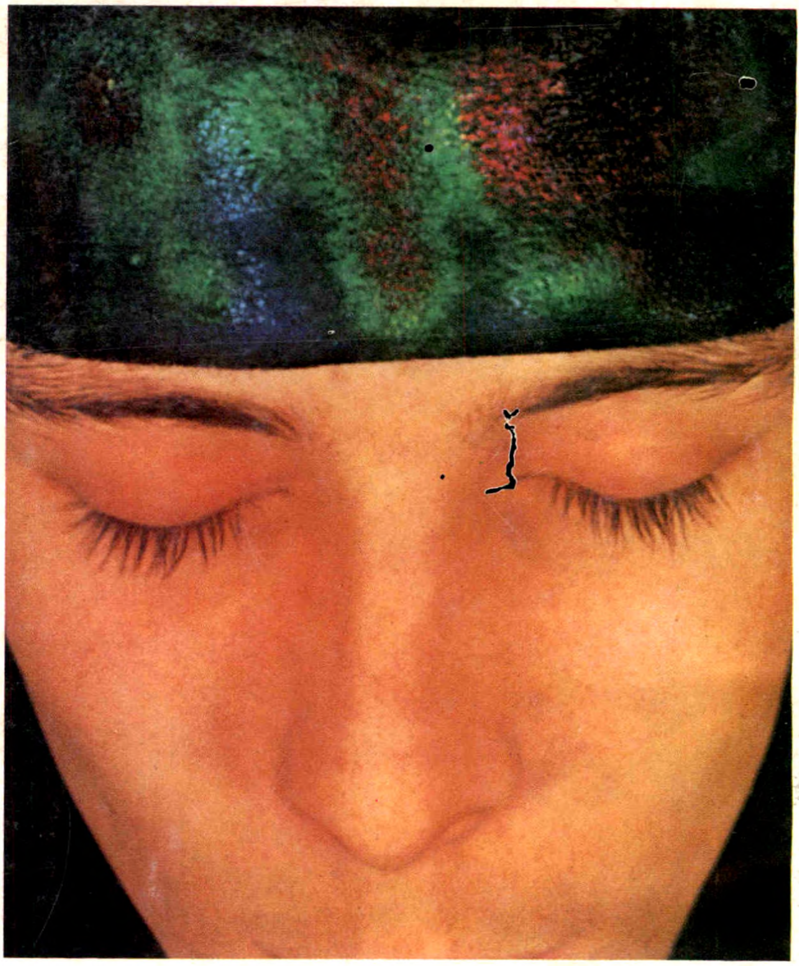
"Seeing migraine headache in its "true colors"



Specific vascular changes are revealed by liquid crystalography

Liquid crystal thermography dynamically demonstrates the unilateral surface temperature changes reflective of the dilation of deep cerebral arteries during a migraine attack. Liquid crystals allow differences in skin temperature to be "mapped" directly on the subject. Variations in skin heat loss are registered immediately, enabling rapid temperature changes to be followed easily. (Red reflects the coolest temperature, then green, blue, and violet.)

This picture was taken of a migraine sufferer during an attack. The colors over the left eye reflect the cooler skin temperature due to the unilateral decreased blood flow to the forehead skin vessels that results from dilation of cerebral vessels on the affected side.

Specific therapy for migraine complicated by tension and G.I. upset

The combined vasoconstrictive actions of ergotamine and caffeine offer the best therapeutic results in helping to abort or relieve the migraine headache. Additionally, belladonna alkaloids help relieve the accompanying gastrointestinal irritability. And the patient's nervous tension, perhaps a precipitating factor in the onset of an attack, is often allayed by the pentobarbital in Cafergot P-B.

CAFERGOT® P-B

TABLETS: Gynergen® (ergotamine tartrate, U.S.P.) 1 mg.; caffeine, U.S.P., 100 mg.; Bellafoline® (levorotatory alkaloids of belladonna, as malates) 0.125 mg.; sodium pentobarbital, U.S.P., (*Warning:* May be habit forming) 30 mg.

SUPPOSITORIES: Gynergen® (ergotamine tartrate, U.S.P.) 2 mg.; caffeine, U.S.P., 100 mg.; Bellafoline® (levorotatory alkaloids of belladonna, as malates) 0.25 mg.; pentobarbital, N.F., (*Warning:* May be habit forming) 60 mg.; inactive ingredients: tartaric acid, N.F., malic acid, lactose, U.S.P., and theobroma oil, U.S.P.

Contraindications: Peripheral vascular disease, coronary heart disease, hypertension, impaired hepatic or renal function, sepsis, and pregnancy. Hypersensitivity to any of the components.

Precautions: Although signs and symptoms of ergotism rarely develop even after long term intermittent use of the orally or rectally administered drugs, care should be exercised to remain within the limits of recommended dosage.

Adverse Reactions: Numbness and tingling of fingers and toes, muscle pains in the extremities, weakness in the legs, precordial distress and pain, transient tachycardia or bradycardia, nausea, vomiting, localized edema, and itching. Drowsiness may occur with Cafergot P-B.

Adult Dosage: *Orally*—Two tablets at first sign of attack; if needed, 1 additional tablet every half hour until relieved (maximum, 6 per attack or 10 per week). *Rectally*—One suppository as early as possible in attack; second in 1 hour, if needed (maximum, 2 per attack or 5 per week).

Overdosage: Symptoms include vomiting; numbness, tingling, pain and cyanosis of the extremities associated with diminished or absent peripheral pulses; hypertension or hypotension; drowsiness, stupor, coma, convulsions and shock. A case has been reported of reversible bilateral papillitis with ring scotomata in a patient who received five times the recommended daily adult dose over a period of 14 days. Treatment consists of induction of emesis, gastric lavage, and catharsis; maintenance of adequate pulmonary ventilation; correction of hypotension; and control of convulsions. Treatment of peripheral vasospasm should consist of warmth, but not heat, and protection of the ischemic limbs. Vasodilator may be used with benefit but caution must be exercised to avoid aggravating an already existent hypotension.

Before prescribing, see package insert for full product information.

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